Investigation into the synthetic potential of ethenesulfonyl fluoride *via* homogenous catalysis

Kimberleigh Bianca Govender

2017

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This thesis is submitted to the School of Health Sciences, College of Health Science, University of KwaZulu-Natal, Westville, to satisfy the requirements for the degree of Master of Medical Science in Pharmaceutical Chemistry.

This is a thesis in which the chapters are written as a set of discrete research papers, with an overall introduction and summary. Typically, these chapters will have been published in internationally recognized ISI-rated peer-reviewed journals.

This is to certify that the contents of this thesis are the original research work of Ms. Kimberleigh Bianca Govender, carried out under our supervision at the Catalysis and Peptide Research Unit, University of KwaZulu-Natal, Westville Campus, Durban, South Africa.

Supervisor:

Signed: _____ Name: **Prof. T Naicker** Date: _____

Co-Supervisor:

Signed: _____ Name: **Prof. T Govender** Date: _____

Co-supervisor:

Signed: _____ Name: **Prof. H. G Kruger** Date: _____

Co-supervisor:

Signed: _____ Name: **Prof. P. I Arvidsson** Date: _____

ABSTRACT

Sulfonyl fluorides are becoming increasingly attractive in both chemistry and biology. Not only does this functional group inhibit several proteins, but several advantages over its Br and Cl counterparts, makes it a useful synthon and "click reagent" for organic synthesis. Despite this, there are very few methods to easily obtain various sulfonyl fluoride derivatives. One particular sulfonyl fluoride containing compound that has received considerable attention in recent literature is ethenesulfonyl fluoride (ESF). This molecule has been used to attach the sulfonyl fluoride moiety onto larger, more complex molecules. Thus, the main objective of this thesis was to investigate some unexplored avenues of the application of ESF in homogenous catalysis in order to easily prepare sulfonyl fluoride derivatives. The transformations and target materials selected would thus be both versatile and indispensable tools for organic synthesis.

To achieve this aim, the use of a transition metal catalyzed reaction was first employed. A palladium catalyzed oxidative Heck coupling reaction was developed using ESF as the substrate. After screening various palladium catalysts, oxidants and bases, a mixture of $Pd(OAc)_2$, $Cu(OAc)_2$ and LiOAc resulted in an effective combination that provided the desired products in good yields (up to 80 %) under mild conditions. The generality of this method was demonstrated by the effective reactivity maintained when screened against a diversity of boronic acids. The usefulness of the products generated from this method was demonstrated by the subsequent development of a novel one-pot preparation of β-sultams. These motifs have otherwise remained elusive to organic synthesis emphasizing the importance of this new approach (**Chapter 2**).

The application of the oxidative Heck method was further investigated as a key step in the preparation of Naratriptan, an effective and popular drug for the treatment of migraines. The attachment of ESF onto the desired indole scaffold was successful, however the remaining proposed steps proved to require additional optimization. It was found that when the β-sultam was treated under basic conditions, a novel ring opening reaction of the β-sultam occurred, which resulted in the formation of vinyl sulfonamides. It was concluded that as a future prospect, hydrogenation of the vinyl sulfonamides be carried out prior to the Aldol condensation in the preparation of Naratriptan (**Chapter 3**).

To fully apply the ESF to homogenous catalysis and to obtain more sulfonyl fluoride derivatives, it's amiability to organocatalysis was also explored. ESF was used as a substrate in a number of Michael reactions in which organocatalysts with various modes of action were applied. It was found that reacting the ESF with methyl 2-oxocyclopentanecarboxylate in the presence of a chiral thiourea catalyst (hydrogen bonding catalysis), showed the best reactivity and yield (96 %). Determining the enantioselectivity of the reaction proved difficult by chiral HPLC, however when the optical rotation was measured, it was found that the reaction was enantioselective (**Chapter 4**). A crystal of the product was grown and analysed, which confirmed the synthesis of the racemate (**Chapter 5**). This proved to be the first instance of an

organocatalyzed reaction where ESF was used as a substrate. These results have confirmed the hypothesis of using ESF within organocatalysis and has led to new opportunities in the search for new sulfonyl fluoride derivatives.

DECLARATION I

Plagiarism declaration

I, **Kimberleigh Bianca Govender** declare that

1. The research work reported in this thesis, except where otherwise indicated, is my original research.
2. This thesis has not been submitted for any degree or examination at any other university.
3. This thesis does not contain other person's data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.
4. This thesis does not contain other person's writing, unless specifically acknowledged as being sourced from other researchers. In cases where other written sources have been quoted:
    a. Their words have been re-written but the general information attributed to them has been referenced.
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Signed

_____

Kimberleigh Bianca Govender

DECLARATION II

Publications

List of Publications

1. **Synthesis of "Dual Warhead" *β*-Aryl Ethenesulfonyl Fluorides and One-Pot Reaction to *β*-Sultams. (Chapter 2) Published**

   Praveen K. Chinthakindi, **Kimberleigh B. Govender**[$], A. Sanjeeva Kumar[$], Hendrik G. Kruger, Thavendran Govender, Tricia Naicker, and Per I. Arvidsson, *Org. Lett.*, 2017, 19(3), pp 480 – 483.

   [$]These authors contributed equally.

   Organic Letters is a highly ranked and prestigious journal within the field of organic synthesis with an impact factor of 6.73.

   Praveen K. Chinthakindi contributed to the design of the project and writing of the publication.
   ***Kimberleigh B. Govender** optimized the reaction conditions, synthesized and characterized all the compounds, and contributed to the writing and editorial of the publication.*
   A. Sanjeeva Kumar synthesized and characterized some of the compounds, and contributed to the writing of the publication.
   The remaining authors are supervisors.

2. **Synthesis, characterization and crystal structure of methyl 1-(2-(fluorosulfonyl)-ethyl)-2-oxocyclopentanecarboxylate, $C_9H_{13}FO_5S$. (Chapter 5)**

   Kimberleigh B. Govender, Marivel Samipillai, Thavendran Govender, Hendrik G. Kruger and Tricia Naicker, 2017, *Kristallogr. NCS. SUBMITTED.*

   ***Kimberleigh B. Govender** synthesized and characterized the compound, grew the crystal and wrote the publication.*
   Marivel Samipillai solved the crystal structure.
   The remaining authors are supervisors.

ACKNOWLEDGMENTS

"I love you, O Lord, my strength"- Psalm 18 verse 1

I would like to express my sincerest gratitude to:

- My Lord and Saviour, Jesus Christ, for His immense strength and mercy throughout my studies. May my work always glorify your name.
- My parents, for their unwavering support, encouragement and tolerance of me during the very stressful days and late nights. This is for you!
- The rest of my family, Candice Harris, Benedict Govender, Warren Harris, Gabrielle Harris and Aaron Harris, for their support and constant words of encouragement, and even for the jokes at times.
- My other half, Sishen Moodley, for his endless support, encouragement and love, especially during those difficult and stressful days.
- My supervisors, Prof Tricia Naicker, Prof Thavendran Govender, Prof Gert Kruger and Prof Per Arvidsson, for their guidance and support throughout my thesis. They have provided me with a bountiful amount of knowledge and skills that not only improved my scientific skills, but helped me to develop as an individual. It has been an honor to work alongside scientists of such great caliber.
- My mentor, Praveen Chinthakindi, for imparting his immense knowledge of chemistry to me and training me to improve my skills as a scientist.
- Dr. Byron Peters, Shimaa Amin and the rest of the CPRU group of 2016-2017, for the advice, laughs and assistance throughout my days in the lab. They have made a profound impact on both my career and life.
- To the technical staff at the University of KwaZulu-Natal for their assistance.
- National Research Foundation (NRF) and the University of KwaZulu-Natal (College of Health Sciences) for financial support.

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CHAPTER 1

Introduction

Background

1. Sulfonyl Fluorides

The sulfonyl fluoride moiety has become increasingly important in both chemical and biological fields. Recently, Sharpless and co-workers described the sulfonyl fluoride moiety as a potential "click reagent,"[1] which refers to the ability of the functional group to readily react under simple conditions.[1] This moiety shows several advantages over its chloride analogue, hence replacing its position in many synthetic schemes. Typically, sulfonyl chlorides are used as precursors to prepare more complex molecules such as sulfonamides[2] and sulfinamides.[3] However, due to the highly reductive nature of the S–Cl bond, whereby the sulfinate ion forms[1] (**Figure 1**), such transformations are often problematic. Recently, Bogolubsky *et al.* showed the advantages of using sulfonyl fluorides over the respective chlorides in preparing sulfonamides.[4]

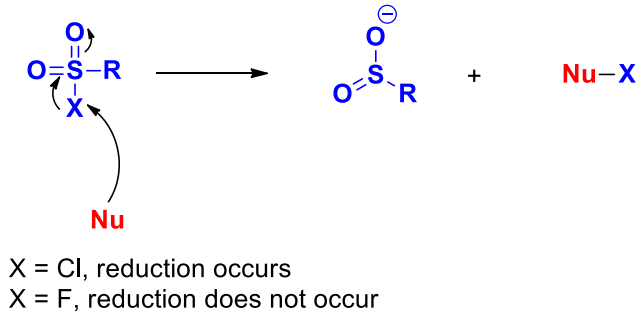
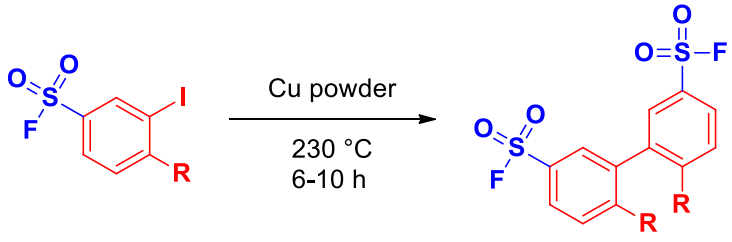


Figure 1: Reductive nature of sulfonyl chlorides and sulfonyl fluorides[1]

In comparison to the chloride moiety, the S–F bond exhibits increased resistance to reduction. This is due to the highly electronegative nature of the fluorine atom, which favours heterolytic bond fission (in favour of F^- generation)[1] and prevents reduction as shown in **Figure 1**. The electronegativity of the fluorine atom also allows for exclusive reactions at the sulfur atom during reactions with carbon nucleophiles, such as with organolithium reagents.[5] This selectivity is not observed with -RSO_2Cl under the same conditions where a mixture of sulfonylation and chlorination products are observed.[1] Likewise, the sulfonyl fluoride group has shown greater stability towards oxidation in comparison to the sulfonyl chloride. This was first shown by Davies and Dick, who found that oxidation of benzylsulfonyl fluorides were only possible if first converted to the chloride analogues.[5]

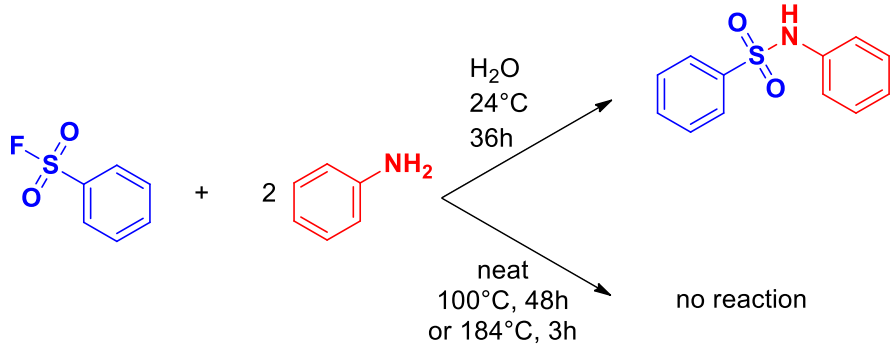
The versatility of the -SO_2F group is further accentuated by its thermodynamic stability.[1] Compounds containing the sulfonyl fluoride group are often able to withstand harsh reaction conditions due to the

functional group's tolerance to hydrolysis and thermolysis.[6] This can be attributed to the significantly larger bond energy of S–F in comparison to other sulfonyl halides. This stability was first shown by Steinkopf *et al*. where aryl compounds containing the sulfonyl fluoride group were subjected to Ullmann couplings under high temperatures (**Scheme 1**).[7] They had found that the chloride analogues decomposed when subjected to the same conditions.



Scheme 1: Stability of the sulfonyl fluoride group at elevated temperatures[7]

However, fluoride ions are typically more reactive than other halide ions, being highly basic in nature and even being able to form a bifluoride ion $(FHF)^-$ in aqueous media.[1, 8] Thus, protic solvents such as water and alcohols are able to activate the sulfonyl fluorides to undergo nucleophilic substitution, as shown in **Scheme 2**. The ability of the sulfonyl fluorides to undergo such reactions in these solvents – unlike the chloride or bromide analogues – has positive implications in green chemistry and furthermore, applications as a covalent "warhead" in chemical biology.[9]



Scheme 2: The effect of fluoride stabilization in water[1]

1.1 Sulfonyl fluorides as warheads in chemical biology

The sulfonyl fluoride moiety as an inhibitor of proteins was first reported by Fahrney and Gold, in which they discussed the role of the functional group to inhibit esterases.[10] Subsequently, the functional group was found to unselectively inhibit a wide range of proteins, which was extensively discussed by Jones and co-workers.[9] The most popular of these protease inhibitors are phenylmethane sulfonyl fluoride (PMSF) and 4-(2-

aminoethyl)benzenesulfonyl fluoride (AEBSF), shown in **Figure 2**. These sulfonyl fluoride containing compounds are used as covalent serine protease inhibitors, where they bind to the free -OH of serine *via* sulfonylation. The inhibition is typically irreversible as the resultant sulfonyl enzyme derivative is stable.[11] Some sulfonyl fluoride molecules are also able to inhibit fatty acid amide hydrolase and thus have direct use in the treatment of pain, inflammation and sleep disorders.[12, 13]

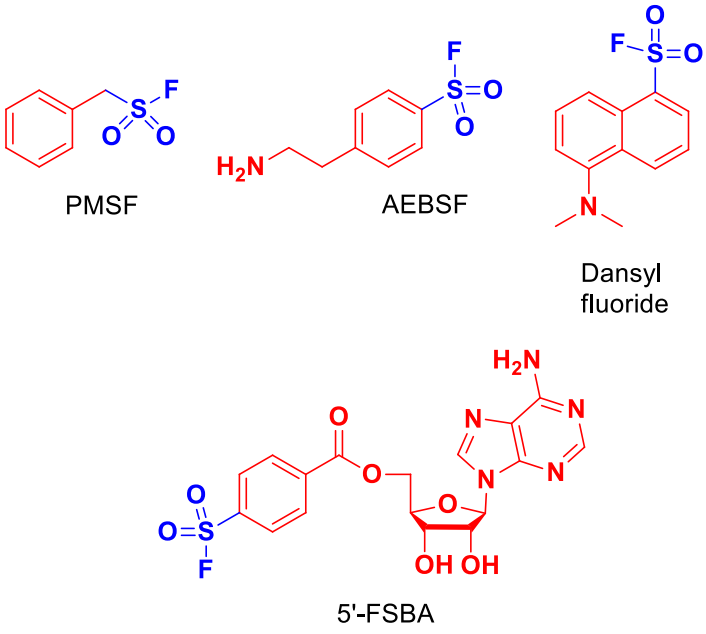


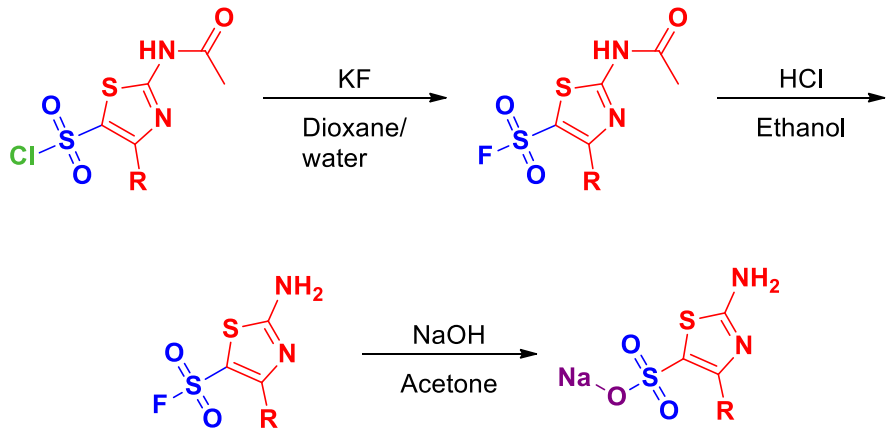
Figure 2: Sulfonyl fluorides applied to protein inhibition and labelling[9]

Since the sulfonyl fluoride group can form covalent bonds with the proteins, many of these compounds have been used to label proteins and binding sites. Dansyl fluoride (**Figure 2**) has been used to label serine proteases, where the sulfonyl fluoride group sulfonates the serine group, rendering a fluorescent molecule.[14] Anees *et al.* were able to apply this principle in labelling proteases bound to tumour cells.[15] In a similar fashion, 5'-(*p*-fluorosulfonylbenzoyl)adenosine (5'-FSBA) and its derivatives have been used to label Adenosine Triphosphate (ATP) binding sites[16] and in doing so improved the studies of protein activity.[17]

1.2 Sulfonyl fluorides as a connector molecule

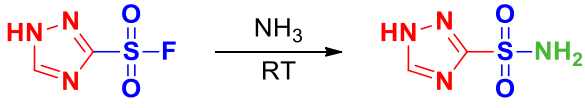
The synthesis of large and/or complex molecules, such as drugs, readily requires molecular units that contain functional groups to attach and facilitate the growth of the backbone towards the target molecule. These molecular units are termed connector molecules.[1] Connector molecules require functional groups that react under essentially orthogonal conditions. Compounds containing the sulfonyl fluoride group are ideal for this purpose. This is due to the stability (weak reactivity) of the moiety in a variety of environments, as mentioned previously.

Its application as a connector molecule was first shown by De Cat *et al.* who synthesized a number of fluorosulfonyl 2-aminothiazoles and then further derivatized these compounds *via* alkaline hydrolysis, yielding alkali sulfonates (**Scheme 3**).[18] It was found that the addition of the fluoride group allowed for further transformations of the 2-aminothaizoles, before it was transformed to an alkali sulfonate.



Scheme 3: Sulfonyl fluoride as connector molecules in the synthesis of alkali sulphonyl 2-aminothaizoles[18]

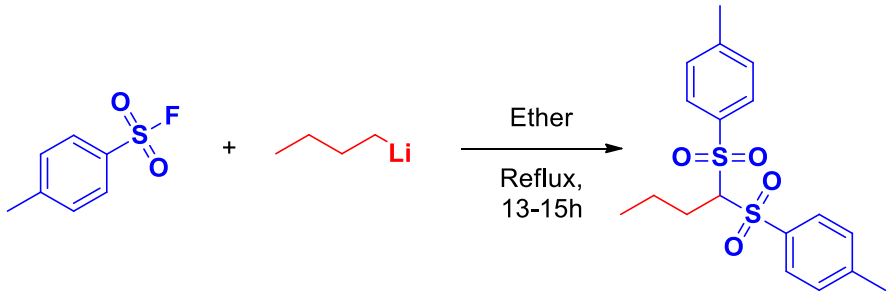
Most of the literature in this field typically describe the various transformations where the sulfonyl fluoride group acts as a substrate. The most popular of the transformations include the replacement of fluoride with a nitrogen atom. This reaction was first described in 1952 by Jensen *et al.* who transformed arylsulfonyl fluorides into sulfanilhydrazide.[19] However, the reaction displayed low reactivity. Subsequently, Revankar and co-workers looked at the formation of heterocyclic sulfonamides from sulfonyl fluorides by a simple reaction with liquid ammonia at room temperature (**Scheme 4**).[20] As mentioned in section **1**, Bogolubsky *et al*. recently described the synthesis of aliphatic sulfonamides by reacting aliphatic sulfonyl fluorides with aliphatic amines.[4] Notably, sulfonyl fluoride showed improved selectivity in the cases where the aliphatic amines contained additional nucleophilic groups.



Scheme 4: Heterocyclic sulfonamides from corresponding sulfonyl fluoride[20]

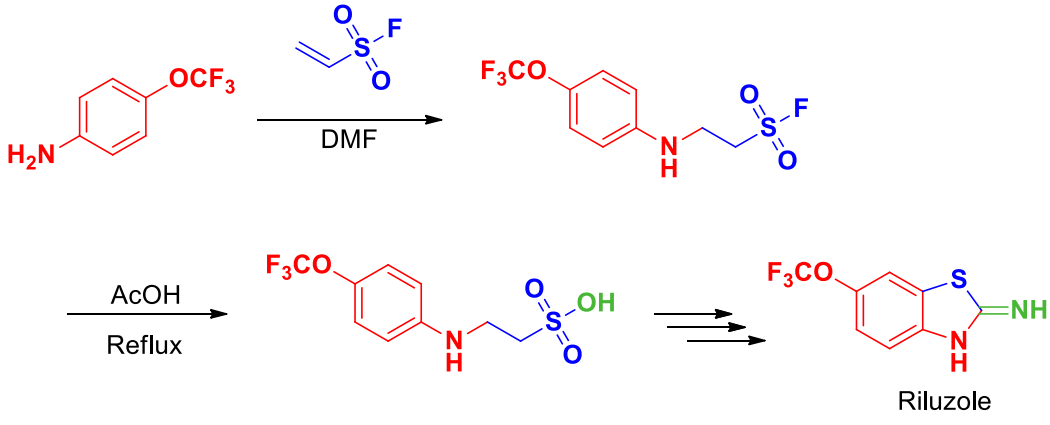
Sulfonyl fluorides have also been applied in the synthesis of sulfonic esters. Rostovtsev *et al.* were able to react tetrafluoroethanesulfonyl fluorides with phenols to obtain tetraflates.[21] These fluorinated aryl sulfonates were then further transformed *via* palladium-catalyzed aminations. The formation of *β*-disulfones is also possible with a sulfonyl fluoride containing molecule. Fukuda *et al.* showed it was possible to prepare these

β-disulfones by reacting *p*-toluenesulfonyl fluoride with various organometallic compounds, such as *n*-butyllithium, as shown in **Scheme 5**.[22]



Scheme 5: Formation of *β*-disulfones from sulfonyl fluorides[22]

The transformations of sulfonyl fluorides also include the formation of sulfonic acids. Jimonet *et al*. displayed the use of sulfonyl fluorides as connector molecules in a step-wise synthesis to form analogues of the drug, Riluzole,[23] which is used to treat motor neuron disease.[24] The sulfonyl fluorides were obtained *via* a Michael reaction between anilines and ethenesulfonyl fluoride (ESF), which was then transformed into the sulfonic acid *via* hydrolysis (**Scheme 6**). The sulfonic acids obtained were then further transformed to obtain the desired analogues.

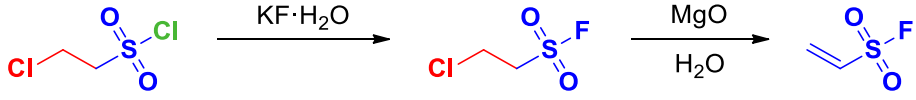


Scheme 6: Use of sulfonyl fluoride as a connector molecule for the synthesis of Riluzole analogues[23]

There are many ways to introduce the -SO_2F group onto larger molecules before it can be further derivatized. One such method involves preparation of the chloride analogue and then converting to the fluoride, as shown by De Cat *et al.* in **Scheme 3**.[18] Alternatively, the -SO_2F group can be added on using smaller -SO_2F containing molecules, such as ESF, the chemistry of which will be discussed in the following section.

1.3 Ethenesulfonyl fluoride

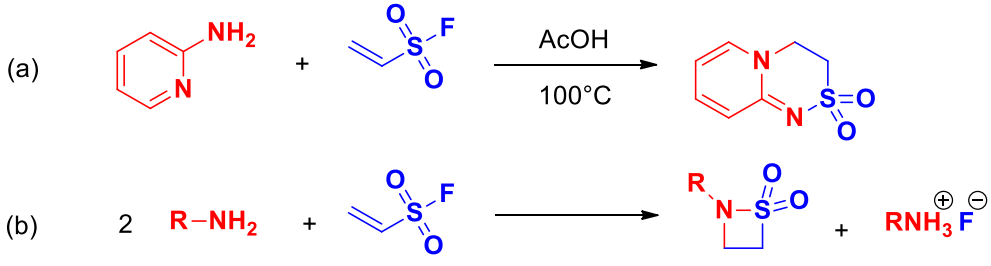
ESF was initially patented in 1953 by Hedrick, where it was prepared by reacting ethenesulfonyl chloride with potassium fluoride in water.[25] It was originally used as a co-polymerizable compound. In 1979, Krutak *et al*. described the synthesis of ESF on a larger scale, as shown in **Scheme 7**. [26] This was when the versatility of ESF was first discovered as it was applied to cycloadditions and heterocyclizations.



Scheme 7: Synthesis of ethenesulfonyl fluoride[26]

Initially the authors looked for methods in which to synthesize several dyes that bared sulfonamide groups. Preliminary experiments with aromatic amines and ethenesulfonamides were unsuccessful. However, when ESF was reacted with the aromatic amines, the desired 2-(*N*-alkylanilino)ethanesulfonyl fluorides were obtained in 100 % yield.[26] The authors then showed the first application of ESF as a connector molecule as the 2-(*N*-alkylanilino)ethenesulfonyl fluorides were further treated with amines to obtain the corresponding sulfonamides. This simple reaction exhibits why ESF is an almost perfect connector molecule. The highly electrophilic double bond can react with a wide range of nucleophiles while the -SO_2F group remains intact. Once reacted the -SO_2F group can then be further transformed. Krutak *et al*. then extended the transformations of these sulfonamides as they were used as precursors for azo dyes.[26]

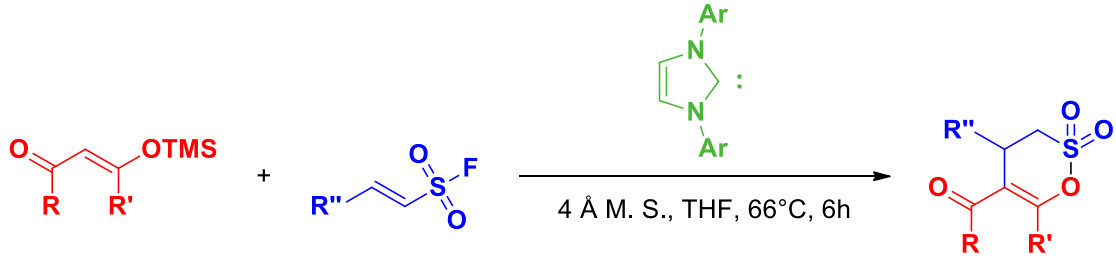
To further extend the chemistry of ESF, in 1979 Krutak *et al*. reacted the compound with 2-aminopyridines, which, to their surprise, resulted in the formation of heterocyclic compounds *viz.* fused 1,2,4-thiazines 1,1-dioxanes (**Scheme 8a**). The authors also looked at the reaction of ESF in Diels-Alder and cycloaddition reactions, in which ESF acts as a highly reactive dienophile. The Diels-Alder reactions of ESF were further elaborated by Daeniker and Druey, where ESF was reacted with cyclopentadienes to afford bicyclic sulfonyl fluorides, which were later converted to bicyclic sulfonamides.[27]



Scheme 8: ESF applied to the formation of heterocycles[27, 28]

Further cyclizations involving ESF were later shown by Chanet-Ray *et al*. who showed that treatment of ESF with two equivalents of primary amine results in the formation of *β*-sultams in high yields (**Scheme 8b**).[28] Since then the literature on ESF has been infrequent. Recently, however, Sharpless and co-workers demonstrated how ESF can be used in the decoration of N, C, and O nucleophiles.[1] The Sharpless group also improved the original synthesis of ESF by replacing the KF used with K(FHF), which resulted in an increase in the yield from 79%[26] to 98%.[29] This has once again sparked interest in this versatile, connector molecule.

In 2015, Ungureanu *et al.* applied ESF and some of its derivatives in the synthesis of *N*-heterocyclic carbenes, which were further applied to the synthesis of *δ*-sultones (**Scheme 9**).[30] Recently, Mayr and co-workers claimed that ESF is the "most perfect Michael acceptor ever found."[31] ESF was treated with sulfonium and pyridinium ylides, and the rate constants of these reactions were determined. The data obtained was then used to determine the electrophilicity parameter of ESF, which when compared to other Michael acceptors, proves to be the best.



Scheme 9: Synthesis of *δ*-sultones from ESF derivatives[30]

Despite these recent advances in ESF chemistry, the molecule has yet to be applied to catalysis, which could further expand its scope and applications. Thus, the main aim of this thesis is to investigate the chemistry of ESF in a range of catalytic reactions, focusing specifically on homogenous catalysis.

2. Homogenous Catalysis

The use of a catalyst to perform a synthetic transformation is fast becoming the norm in organic synthesis.[32-34] Catalysts are molecules that are employed to increase the rate of the reaction, by decreasing the activation energy of the reaction, without being consumed itself. Catalysts typically have a kinetic effect whereby they help to reduce the activation energy required for the formation of products.[35] Over the years, the scope of a catalyst has been extended as catalysts now serve to cause the reaction to follow certain pathways, or result in regioselective, stereoselective or chemoselective products.[36]

Catalysis can be broadly divided into two categories *viz.* heterogeneous and homogeneous catalysis. Heterogeneous catalysis refers to catalysts that are often in a different phase as compared to the reagents. Conversely, homogeneous catalysts are in the same phase as the reagents, typically in solution. Homogenous

catalysis, which is the focal point of this thesis, can be subdivided into two subcategories *viz.* transition metal catalysis and organocatalysis. This thesis aims to look at both as applied to the use of ESF as a substrate in various reactions.

2.1 Transition Metal Catalysis

The use of transition metals in catalysis can offer a great number of advantages.[37, 38] The presence of typically unfilled *d* orbitals lends itself to several characteristics, such as the ability to form five or six bonds, exist in various oxidative states, and allow for coordination of a multitude of ligands. The coordination of ligands allows for further features, as the coordination of specific ligands can alter the behaviour of the transition metal in terms of sterics and electronics.[39] These features allow transition metals to be applied to a wide variety of reactions.[40] The most common of which involves cross-couplings that result in the formation of carbon-carbon and carbon-heteroatom bonds.[41] For the purpose of this thesis, palladium catalyzed reactions will be discussed further.

2.1.1 Palladium Catalyzed Reactions

One of the most widely used transition metals for the formation of carbon-carbon and carbon-heteroatom bonds, is palladium (Pd). First discovered in 1803,[42] Pd has since been extensively studied and applied to organic synthesis of fine chemicals[43] and pharmaceutics.[44] Pd catalyzed reactions are advantageous as they afford products in high yields and with good regio-, stereo- and chemoselectivity, which has resulted in its application toward the synthesis of complex biological compounds.[45] The use of Pd in cross-coupling reactions recently earned Richard F. Heck, Akira Suzuki and Ei-ichi Negishi the 2010 Nobel prize in Chemistry, for their development of a variety of eponymously named, Pd catalyzed C-C bond forming reactions (**Figure 3**).

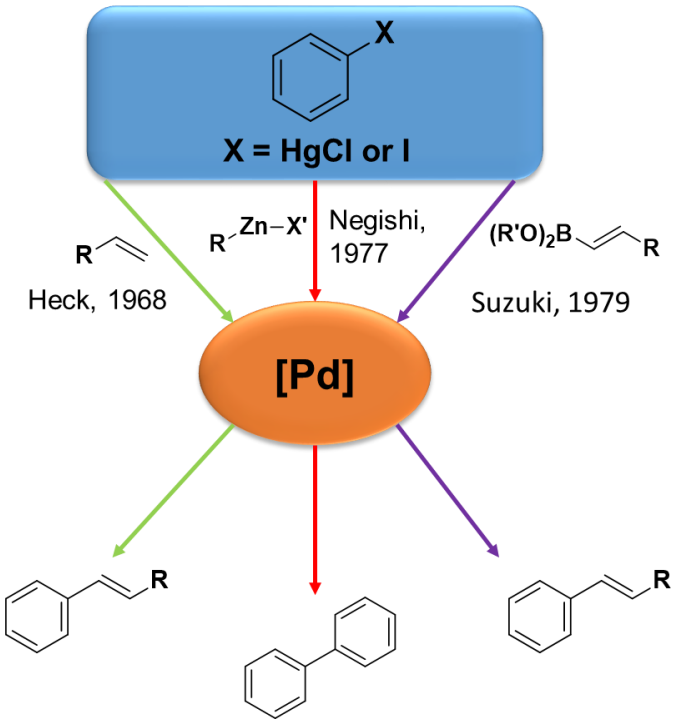


Figure 3: Nobel winning Pd catalyzed cross-coupling reactions[45]

The widespread application of Pd as a catalyst is attributed to its ability to readily participate in reversible two-electron oxidation and reduction.[46] Pd typically exists in Pd(0) and Pd(II) oxidative states, each of which are used for different catalytic transformations. Pd(II) is used for alcohol or allylic oxidation whereas Pd(0) is applied to cross-coupling reactions.[47] However, a majority of Pd catalytic cycles involves an interplay of Pd(0) and Pd(II).

The most applied and researched Pd catalyzed cross-coupling reaction is the Heck, or more commonly known as Mizoroki-Heck reaction, which has become a sharpening stone for Pd-catalysis.[48] Discovered independently by Mizoroki[49] in 1971 and by Heck[50] in 1972, this reaction has now become the reaction of choice for affording new carbon-carbon bonds, including the formation of tertiary and quaternary stereogenic centres.[45] The Mizoroki-Heck reaction can be defined as the reaction between sp^2 aryl or alkenyl halides and alkenes that affords a substituted alkene product. There are many derivatives of the Mizoroki-Heck reaction, one such example is the oxidative Heck, which forms part of the work in this thesis.

2.1.1.1 The Oxidative Heck Reaction

The oxidative Heck reaction is the green alternative to the Mizoroki-Heck reaction, whereby it employs organoboronic acids in place of aryl halides. Initially reported in 1975 by Heck and Dieck, where vinyl boronic acids were reacted with methyl acrylate and stoichiometric amounts of Pd.[51] The reaction was only

made catalytic in 1994 by Cho and Uemura.[52] Further improvement was made by Kosugi and co-workers in 2001, where the use of a re-oxidant or co-catalyst, *viz.* $Cu(OAc)_2$ was applied.[53] Apart from the change in reactant, the oxidative Heck usually differs in that the reaction is catalyzed by Pd(II) instead of Pd(0), which is typical of the Mizoroki-Heck reaction.

The alteration of the catalyst results in a subsequent change in the catalytic cycle. For the Heck reaction, the first step in the catalytic cycle is oxidative addition of Pd into the carbon halide bond, whereas for the oxidative Heck, this is replaced by a transmetallation step of the boronic acid onto the Pd(II) species (**Figure 4**). In addition, the oxidative Heck reaction does not require the use of base, but rather an oxidant is used to regenerate the catalyst. The most useful oxidant is molecular oxygen, which is environmentally benign.[54]

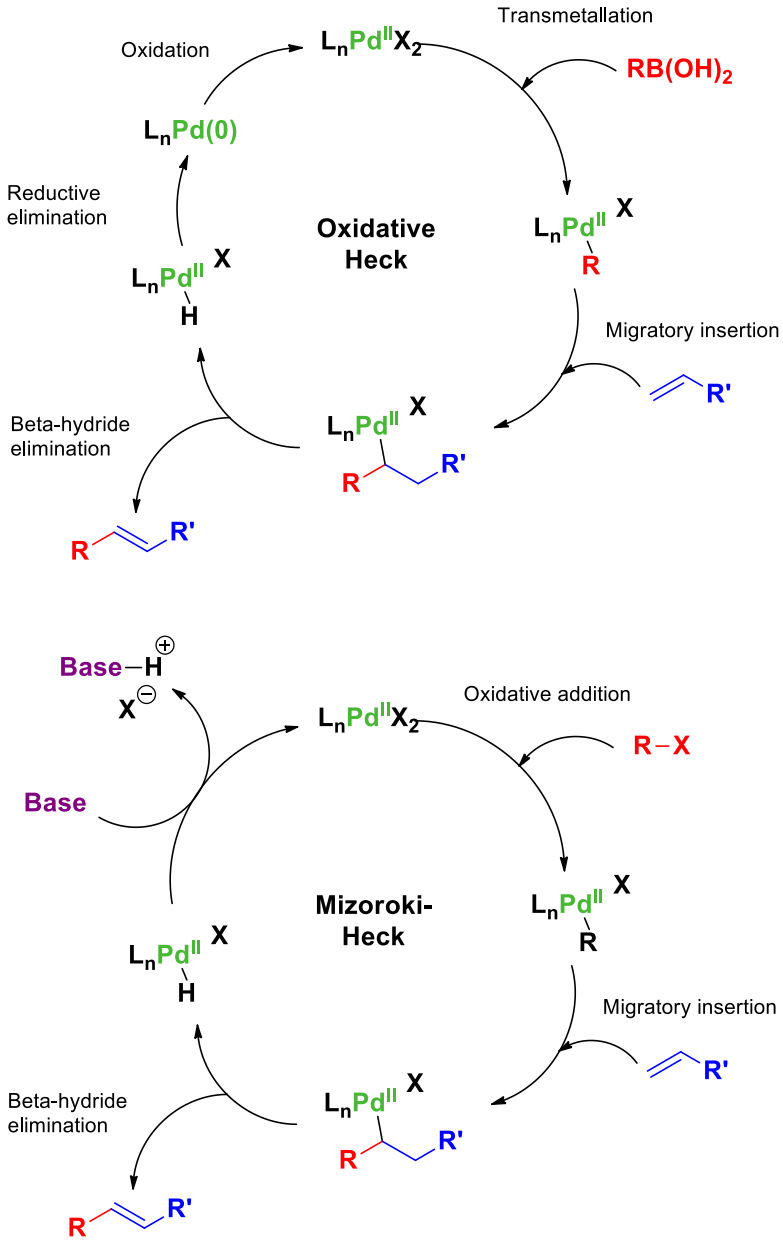


Figure 4: Comparison of Mizoroki-Heck and oxidative Heck catalytic pathways[55]

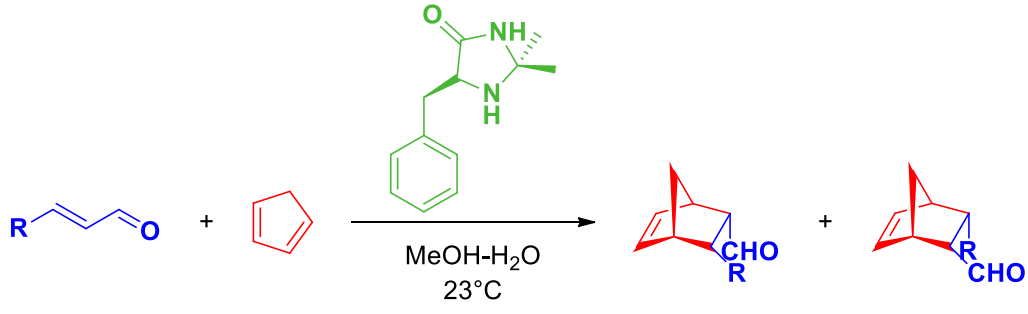
The use of organoboronic acids is also seen as environmentally beneficial as these have low toxicity, high atom economy, commercial availability, and stability in moisture and air.[56] The use of oxidants and Pd(II) catalysts results in milder reaction conditions capable of reacting with problematic alkenes, which is not possible under Pd(0) Mizoroki-Heck conditions.[57] Pd(II) is also beneficial in the oxidative Heck as both N- and P-based ligands can be used. The enantioselective properties of the oxidative Heck reaction was first shown by Mikami and co-workers, where various N- and P-bidentate ligands were used.[58] The application of the oxidative Heck in enantioselective reactions were recently extensively reviewed and documented by Lee.[55]

The efficiency of the oxidative Heck has been improved over the years with the addition of microwave heating. Larhed and co-workers first reported this development in 2003, where the addition of microwaves reduced reaction times to ~15 minutes whilst producing excellent yields.[56] The oxidative Heck reaction has also been applied to a continuous flow method by the same group.[59] This application resulted in a further decrease of the reaction time, while allowing the reaction to be directly scaled-up. The scope of the reaction has also greatly increased over the years where it can be applied to electron rich electron poor and neutral olefins. The extension has been applied to aryl carboxylic acids, arylsilanols, aryl phosphonic acids, and many others used in place of the arylboronic acids.[60] Thus showing the vast applications of the oxidative Heck reaction. Based on this, and the many afore mentioned advantages of the oxidative Heck reaction, one of the aims of this thesis is to apply ESF as the alkene substrate in an oxidative Heck reaction.

2.2 Organocatalysis

Organocatalyzed reactions generally involve the use of organic, non-metal containing molecules as catalysts.[61] The use of organocatalysts was first reported in 1971 by Wiechert and co-workers, who added natural amino acids in place of base in a Michael reaction between vinyl ketones and cyclic diketones.[62] This was done as a means of inducing chirality onto the product, which were to be used as precursors for the synthesis of steroids. It was found that the configuration of the amino acid used directly determined the configuration of the product.

The term organocatalysis was only coined in 2000 by MacMillan, who performed the first enantioselective Diels-Alder reaction (**Scheme 10**).[63] This was carried out by reacting *α, β*-unsaturated aldehydes and dienes in the presence of various chiral amines. Thus, the cycloaddition products were obtained with good selectivity. Subsequently, the application of small chiral molecules in the formation of new chiral molecules has increased exponentially, as depicted in **Figure 5**, and has now become an invaluable tool in the total synthesis of many drugs.[64]



Scheme 10: The first enantioselective Diels-Alder reaction[63]

The main attraction towards organocatalysis are the many advantages that follow it, such as the stability of the organocatalysts in air and moisture, ease of synthesis from commercially available materials and most importantly, its low toxicity, which is in stark contrast to organometallic catalysis.[36] Organocatalysis can also be described as diverse since there are various mechanisms by which they can catalyze a reaction.[65] The organocatalysts can act as a type of Lewis acid/base where it is involved in activation and not consumed during the reaction, or it could form reactive intermediates. Organocatalysts can also be applied to phase-transfer catalysis where it can be used to transport the substrate from one solution phase to the other by means of forming a complex.

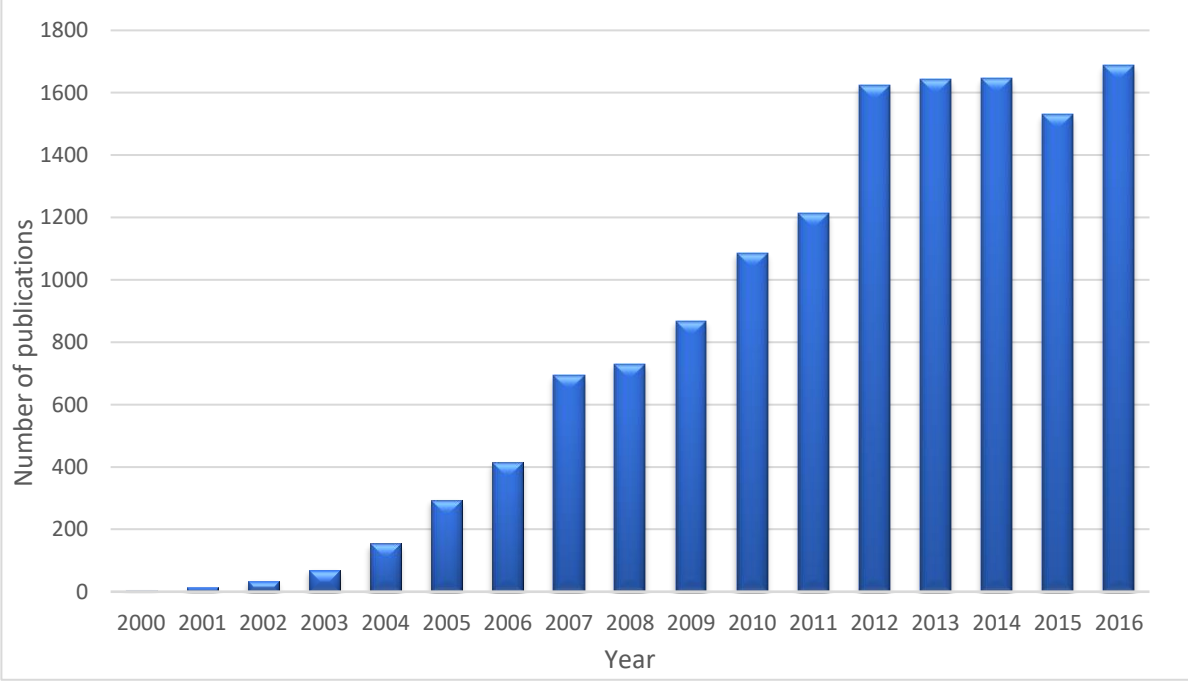


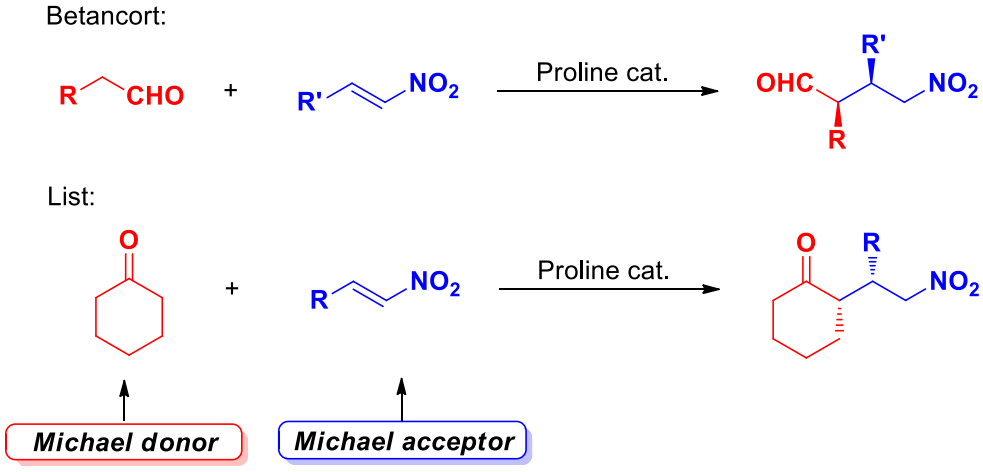
Figure 5: Number of publications containing the word 'organocatalysis' in the title or abstract since 2000 from Scifinder as of January 4, 2017

Due to the versatility of organocatalysts, there are a vast array of reactions to which they can be applied such as Aldol condensations, ring opening reactions, and asymmetric conjugate additions *viz.* Michael reactions, which is one of the focal points of this thesis.[66]

2.2.1 Organocatalyzed Asymmetric Michael Reactions

The asymmetric Michael reaction is one of the most applied reactions in organocatalysis in the formation of new chiral C-C bonds.[67, 68] A Michael reaction can be defined as the conjugate addition of a nucleophile or carbanion (Michael donor) to an electrophile, typically an *α, β*-unsaturated carbonyl compound (Michael acceptor). In organocatalysis, the scope of the Michael acceptor was greatly increased over the years, where

the very reactive nitro-olefins have been the most utilised. The interest in this Michael acceptor first began in 1981 when Seebach and Goliński reacted the nitro-olefins with achiral enamines and obtained the addition products with good diastereoselectivity.[69] The reaction was made catalytic independently in 2001 by List[70] and Betancort,[71] where chiral proline and pyrrolidines were applied as catalysts respectively (**Scheme 11**).



Scheme 11: First organocatalyzed Michael reaction[70, 71]

Since then the development of the organocatalyzed Michael reaction with nitro-olefins has greatly increased. The development has seen many different organocatalysts employed to the reaction to improve the enantioselectivity. Zhange and co-workers reacted nitro-olefins with aldehydes and replaced the typical proline based catalysts with chiral perhydroindolic acid.[72] As a result they were able to obtain *ee*'s (enantiomeric excess) of up to 95%. Luo and Cheng were able to apply chiral ionic liquids as an organocatalyst to the addition of nitro-olefins to aldehydes and ketones.[73] Apart from an adaption of green chemistry, the reaction resulted in *ee*'s of up to 99%.

The Michael addition of nitro-olefins has also been applied with thiourea based catalysts. The presence of two oxygen atoms allows for activation by the acidic protons of the catalyst through hydrogen-bonding interactions. Takemoto and co-workers first showed the dual activation of both the nitro-olefin and the nucleophile using chiral thiourea based catalysts. They added a chiral amine onto a thiourea backbone to activate the nucleophile, resulting in the Takemoto catalyst (**Figure 6**). As a result, they were able to obtain the Michael adducts with up to 95% *ee* and with high reactivity.[74]

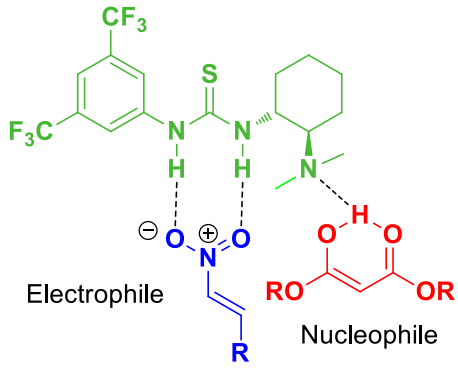


Figure 6: Takemoto's catalyst showing dual activation of electrophile and nucleophile[74]

The use of this dual activation thiourea catalysts typically results in greater control of the stereochemistry of the products. Barbas and co-workers were also able to apply the thiourea catalyst to the Michael addition of nitro-olefins to sterically difficult oxindoles with *ee* up to 90%.[75] The authors then tested the absolute stereochemistry of the reaction by applying it to the synthesis of (+)-physostigmine, a drug used for the treatment of glaucoma.[76] Enders *et al*. applied the use of the thiourea catalyst in a domino Michael-lactonization reaction towards the synthesis of functionalized chromans, where they were able to obtain overall *ee* of up to 99%.[32] Based on the many possibilities that the Michael reaction offers in the field of organocatalysis, and since ESF is described as the "perfect Michael acceptor,"[31] another aim of this thesis was to apply the ESF as a substrate in an organocatalyzed Michael reaction.

3. Analytical and Purification Techniques

Friedrich Engels put it plainly when he said, "without analysis, no synthesis."[77] Analytical tools are vital in synthesis as they assist the chemist in determining whether and how a reaction proceeds and the type of products that result. The purification of compounds is also vital for the analysis. Several analytical methods were used to monitor the multistep syntheses described for this thesis, as well as purification methods for the compounds obtained. The three main techniques used will be discussed further.

3.1 Column Chromatography

Discovered in 1903, chromatography has now become the most important tool in a synthetic chemist's analytical arsenal.[78] It offers a simple way to separate a mixture of compounds into its composite parts. Chromatography works on the principle of selective adsorption,[79] whereby the different components will adsorb onto a stationary phase. Each compound will interact with the stationary phase differently based on their electrostatic nature and molecular size and thus will elute at different times (retention time), as a mobile phase is passed through to aid with elution.[80] There are various different chromatographic methods which differ in both the stationary and mobile phases.

For benchtop gravity column chromatography, the stationary phase is most commonly either silica gel or neutral aluminium oxide and the mobile phase is a solvent or mixture of solvents. The stationary phase is packed into a column and the mixture of compounds to be separated is loaded onto the stationary phase using a suitable solvent. The solvent is then continuously passed through the column. Column chromatography works on the polarities of compounds. Polar compounds interact strongly with the polar stationary phase and typically adsorb on the upper parts of the column, while non-polar compounds interact weakly, hardly adsorbing to the stationary phase.[79] Thus, as the mobile phase, which is usually non-polar solvents, passes through the non-polar compounds elute first from the column . The more polar compounds elute after, typically as the polarity of the mobile phase is increased. The use of a polar stationary phase and a non-polar mobile phase is known as normal phase chromatography, and is the most used method for the purification of compounds. This is a basic summary of column chromatography, for more information the reader is referred to relevant books on this topic.[78-80]

3.2 Nuclear Magnetic Resonance Spectroscopy

Since this thesis was centred around multi-step organic synthesis, a basic overview of Nuclear Magnetic Resonance (NMR) spectroscopy will be highlighted. NMR spectroscopy was discovered independently by two groups in 1946[81, 82] and since then it has become an indispensable tool for the synthetic chemist. By means of NMR spectroscopy, a chemist can characterise the absolute structure of most compounds. NMR spectroscopy works on the magnetic properties of the nuclei of atoms. Those nuclei with an odd number of protons and neutrons (*e.g.* ^{1}H, ^{13}C, ^{19}F, *etc*.) have magnetic properties and can generate its own magnetic field when they spin. When these spinning nuclei are placed in an applied magnetic field ($\mathbf{B_0}$) their magnetic fields can either align with or against the applied field.[83] Those nuclei that align with the applied field have a higher energy state than those that align against it. This creates a difference in energy between the two spin states ($\Delta\mathbf{E}$).[83] When a sample is applied with energy equal to $\Delta\mathbf{E}$ it causes the nuclei to flip between the two energy states and generates a signal. In Fourier Transform NMR (FT-NMR), the sample is placed in a constant magnetic field and excited in short pulses with a radio frequency (rf). The rf pulse applied covers a range of frequencies and thus provides the $\Delta\mathbf{E}$ necessary to excite various nuclei, flip their spin and produce a signal.[84] The signal produced is known as the free induction decay (FID), which decreases over time as the nuclei lose the energy from the rf pulse. A computer receives this signal and displays this as an FID spectrum (**Figure 7**) which is then converted *via* a mathematical equation known as a Fourier Transform.[84] This results in an FT-NMR spectrum, as shown in **Figure 7**.

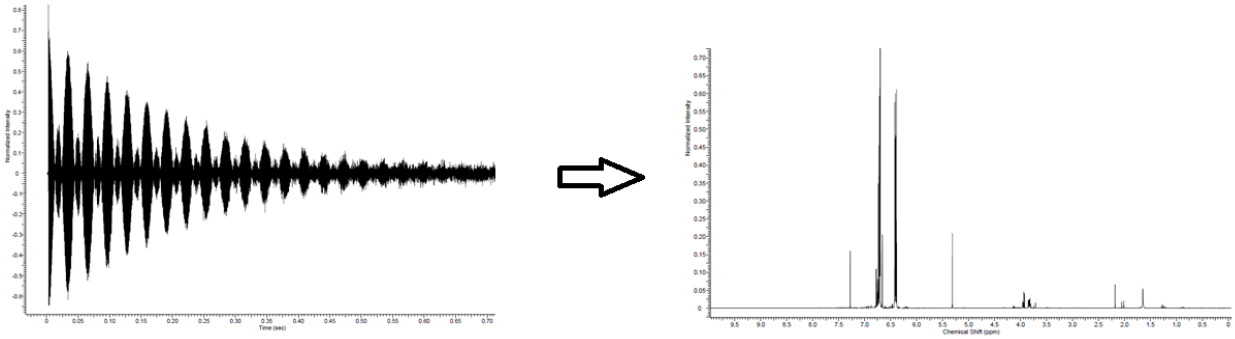


Figure 7: The FID spectrum (left) and the FT-NMR spectrum (right) generated by the FT NMR

Each signal produced in the FT-NMR spectra provides characteristic information about the compound. For proton (^{1}H) NMR the number of signals generated indicates the number of chemically different protons. Those protons that are chemically equivalent *i.e.* in the same chemical environment, produce the same signal and the area under the generated signal indicates the number of protons producing that signal. Where the signal appears on the spectrum provides information about the type of atoms to which the proton is bonded. The nuclei of atoms are surrounded by clouds of electrons, which shields it from the applied magnetic field. The electron environment and the shielding is thus different for various molecules, which effects where the generated signal will appear on the NMR spectrum. Typically, a reference compound is used, such as tetramethylsilane (TMS) and all signals generated are positioned on the spectrum in relation to the reference compound, this is known as the chemical shift. It is this chemical shift that is affected by the electron environment of the molecule, thus each NMR spectrum generated is unique. There are characteristic chemical shifts for certain bonds, which make identification and elucidation of a compound simple. This description of NMR spectroscopy is a basic summary, for more detailed information the reader is encouraged to look up the various books[83-87] and reviews[88, 89] on this topic as well as the many applications of NMR spectroscopy.[90-92]

3.3 Gas Chromatography Mass Spectrometry

During the course of this thesis gas chromatography mass spectrometry was used as the main tool to monitor the reactions, hence a brief overview of this technique will be highlighted. Gas chromatography (GC)- mass spectrometry (MS) is a combination or hyphenated analytical technique that combines the separation technique of GC with the analytic technique of MS. In gas chromatography, a compound or mixture of compounds is vaporized at high temperatures such that they become gases. These gases are then passed through a column (**Figure 8**) by aid of a mobile phase, which is typically an inert gas such as helium. The mobile phase goes through a stationary phase or column that contains a chemical coating, which interacts with the passing compounds and is housed in a temperature controlled oven.[93] Each compound will interact

differently with the column and will elute with different retention times. Since this separation technique depends on the vaporization of compounds, it is typically used for low molecular weight compounds, as these tend to have lower boiling points.[94] The separation of the compounds also depends on the degree of volatility as those with high volatility with travel faster through the column as compared to those with low volatility

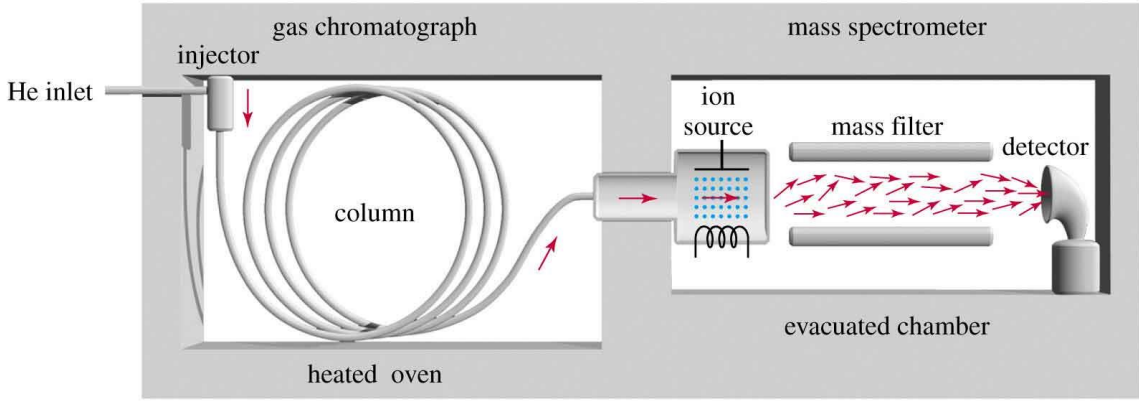


Figure 8: Schematic of a typical GC-MS[95]

The separated compounds by the GC are carried into the MS by the carrier gas. Within the MS, the compounds first become ionized typically by passing the compounds through a stream of electrons. During the ionization process, the compounds break up into charged fragments and these charged fragments pass through a mass filter or mass analyser, as shown in **Figure 8**. The mass analyser separates the fragments based on their mass to charge (m/z) ratio and similar m/z are then carried to the detector. The detector "counts" the number of ions with the same m/z and produces a signal. The signals are combined by a computer, which produces a spectrum. With the MS, one can determine the molar mass of the compound and the structure of the compound based on its fragmentation pattern. ESF and its derivatives are low molecular weight compounds and thus should have low boiling points. Hence GC-MS was chosen as the preferred method for analysis and monitoring of the reactions. The above description is a basic explanation of the principles of GC-MS, for a more detailed understanding the reader is encouraged to view the detailed books[93, 96, 97] and reviews[98, 99] on this topic.

4. Research Questions

I. Can ESF be used as a substrate in a metal catalyzed oxidative Heck reaction?
II. If so, what is the scope of the reaction?
III. Can any resulting products be transformed into more complex biologically important molecules?
IV. Can ESF be used as a substrate in an organocatalyzed Michael reaction?

5. Research Objectives

I. To develop a metal catalyzed oxidative Heck reaction for the synthesis of sulfonyl fluorides derivatives using ESF as a common denominator.

II. To expand the scope of the optimized oxidative Heck methodology.

III. To transform the novel sulfonyl fluoride derivatives from the oxidative Heck reaction in the preparation of highly sought after biologically active compounds.

IV. To develop an organocatalyzed Michael reaction using ESF as a substrate for the synthesis of sulfonyl fluoride derivatives.

6. Outline of thesis

The development and application of homogenous catalytic methods using ESF as a substrate was the main aim of this thesis. The development and scope of an oxidative Heck method applied to ESF is described in **Chapter 2**. The application of the oxidative Heck method toward the synthesis of a biologically active compound, Naratriptan, is described in **Chapter 3**. **Chapter 4** describes the organocatalytic methods applied to ESF and in **Chapter 5** a crystallographic paper is presented. The crystal was obtained from compounds synthesized in **Chapter 4**. With exception to **Chapters 3** and **4**, the remaining chapters of this thesis have been published and submitted in international peer reviewed journals.

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CHAPTER 2

A Synthesis of "Dual Warhead" β-Aryl Ethenesulfonyl Fluorides and One Pot Reaction to β-Sultams

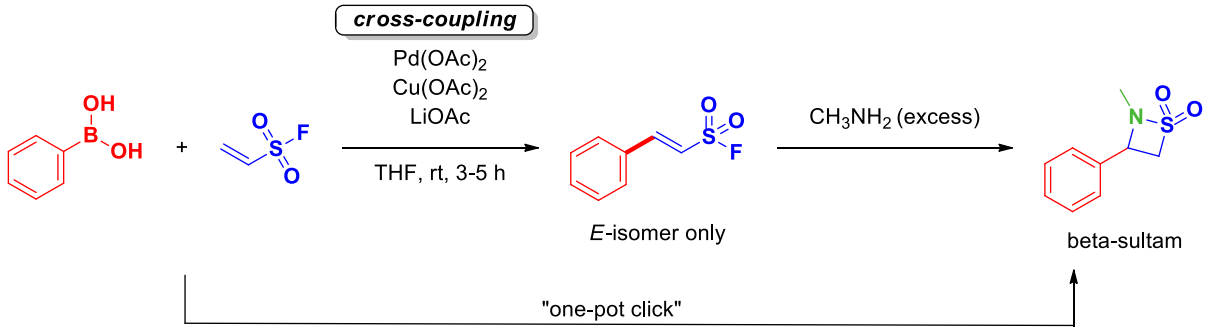
Praveen K. Chinthakindi[§], Kimberleigh B. Govender[§, $], A. Sanjeeva Kumar[§, $], Hendrik G. Kruger[§], Thavendran Govender[§], Tricia Naicker[§], and Per I. Arvidsson[*§†]

[§]Catalysis and Peptide Research Unit, University of KwaZulu-Natal, Durban, South Africa

[*†]Science for Life Laboratory, Drug Discovery & Development Platform & Division of Translational Medicine and Chemical Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

[$]Authors equally contributed

Abstract



Herein, we report an operationally simple, ligand, and additive free oxidative boron-Heck coupling that is compatible with the ethenesulfonyl fluoride functional group. The protocol proceeds at room temperature with chemo and *E*-isomer selectivity, and offers facile access to a wide range of β-aryl/heteroaryl ethenesulfonyl fluorides, which are known to display two electrophilic sites towards *e.g.* enzyme bound nucleophiles. Furthermore, we demonstrate a "one-pot click" reaction to directly access aryl substituted β-sultams – another group with potential as activity based reactive probe and as covalent enzyme inhibitor.

Introduction

Palladium catalyzed oxidative carbon-carbon bond formation reactions are vital in the synthesis of complex organic molecules. A variety of Pd catalyzed reactions have been developed for the arylation of olefins such as Mizoroki-Heck, Meerwein arylation, Heck–Matsuda, and oxidative boron-Heck *etc*. Approaches using an oxidative boron-Heck coupling are becoming increasingly attractive for modern organic syntheses[1] as they offer a wide range of advantages such as efficiency, mild reaction conditions, good functional group tolerance, and widespread applications.[2] In particular, the organoboronic acids used as nucleophiles offer many advantages, as they are moisture and air stable, have low toxicity, and a large variety are commercially available.[3] Recently our group developed a Pd catalyzed cross-coupling method between organoboronic acids

and halo aryl sulfonyl fluorides.[4] The interest in the sulfonyl fluoride (SF) group was sparked by its recent inclusion as a "click reagent" by the Sharpless laboratory[5] as well as privileged "warheads" for covalent enzyme inhibition by Lyn and co-workers.[6, 7] Moreover, Andrey *et al*. explored sulfonyl fluorides as an alternative to sulfonyl chlorides[8] and Matthew *et al*. investigated SFs (PyFluor) as a selective deoxy fluorination reagent.[9] Also, one report has revealed the usefulness of the SF functional group as a PET agent in radio pharmaceuticals.[10] Yet, despite these SFs having many applications in material science,[11-13] the full potential of SFs as building block/intermediates in organic syntheses is yet to be fully realized.

Most recently, Liskamp *et al*. proposed peptide-derived vinylic sulfonyl fluorides as a new class of bielectrophilic warheads for covalent drug discovery which selectively inhibited the threonine residue in the proteasome active site, **Figure 9**.[14] Based on this report, we became interested in the use of ethenesulfonyl fluoride (ESF)[15] as a starting material for such probes, as it is known to be a good connector,[5, 16] Michael acceptor[17] as well as a Diels–Alder dienophile.[18]

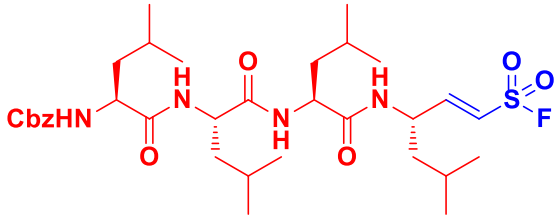
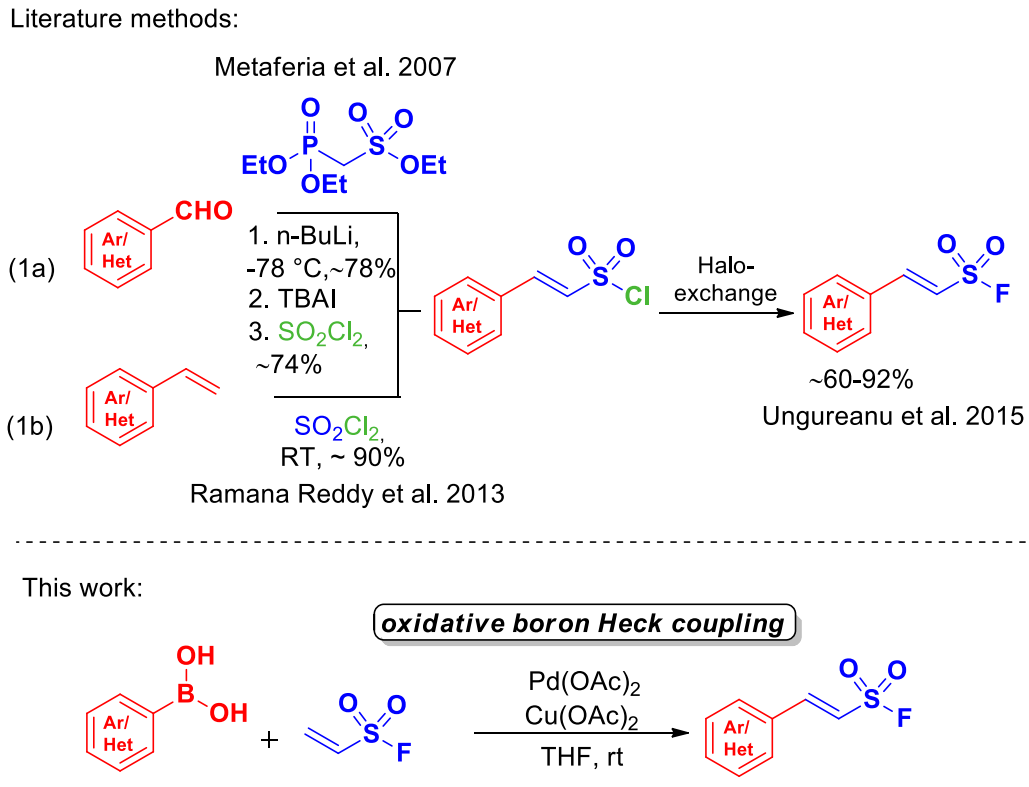


Figure 9: Peptide vinyl sulfonyl fluoride proteasome inhibitor as reported by Liskamp et al.[11]

Albeit useful in a wide range of pharmaceutical and material intermediates synthesis,[15, 19-21] the synthetic procedures to access substituted ethenesulfonyl fluoride derivatives require multistep syntheses (**Scheme-12a, b**) and suffer from disadvantages such as the use of highly pyrophoric (*n*-BuLi),[22] toxic and corrosive reagents ($SOCl_2$).[23,19] Therefore, approaches that use simple and commercial starting materials, such as ethenesulfonyl fluoride and aryl boronic acids (cross-coupling), in a single step would be highly advantageous. This method could be a valuable addition to transition metal catalyzed late-stage functionalization[24] and bioorthogonal chemistry.[25, 26]



Scheme 12: Synthesis of *β*-aryl ethenesulfonyl fluorides

Our earlier findings on palladium catalyzed cross-coupling development [4, 27-29] [4, 7] inspired us to carry out Pd catalyzed arylation of ESF. Herein we report the first and efficient ligand-free oxidative boron-Heck coupling reaction to potentially access a diverse library of aryl substituted ethenesulfonyl fluorides. The obtained ethenesulfonyl fluorides are handy building blocks for consequent synthetic transformations.[30] Until the finalization of this work, this was the first method where ESF was used directly as a coupling partner in Pd catalyzed reactions. However, it should be noted that while we awaited HRMS data of our products, a report from the Sharpless group appeared that describes the synthesis of *β*-aryl ethenesulfonyl fluoride derivatives from arenediazonium tetrafluoroborates and ethenesulfonyl fluoride using a palladium catalyzed Heck–Matsuda cross-coupling reaction.[30] Our work presents the synthesis of *β*-aryl ethenesulfonyl fluoride derivatives from stable and commercially available aryl boronic acids and demonstrates the utility of the resulting *β*-aryl ethenesulfonyl fluoride as starting materials for a mild one-pot synthesis of *β*-sultams that are otherwise difficult to access.

Results and Discussion

To find a suitable catalytic system for the arylation of ethenesulfonyl fluoride, a model reaction with phenyl boronic acid and ethenesulfonyl fluoride was investigated using the oxidative boron-Heck conditions reported by Jung and co-workers, *i.e*. $Pd(OAc)_2$, O_2 and Na_2CO_3 in DMF at 50 °C.[31] However, under these conditions we observed the formation of undesired homocoupling as the major product with only a trace amount of the desired product (8%). Therefore, we attempted to optimize the reaction conditions by evaluating various Pd catalysts {*i.e.* $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$ and Pd-C}; however, this did not improve the reaction yield. We then shifted our focus to explore various oxidants {*i.e.* $Cu(OAc)_2$, DDQ, O_2 and Air}, and bases {NaOAc, Cs_2CO_3, DIPEA, TEA} (**Table 1**). In the presence of DDQ as the oxidant no product formation was observed (data not shown). Similarly, air oxidation (data not shown) and O_2 offered only low yields (**Table 1, entry 1**). However, in the presence of stoichiometric amount of $Cu(OAc)_2$, good improvement of yield was observed (**Table 1, entry 2**); this is due to good synergy between Pd and Cu in the catalytic cycle,[32] which is known to enhance the rate of the oxidation of Pd(0) to Pd (II).

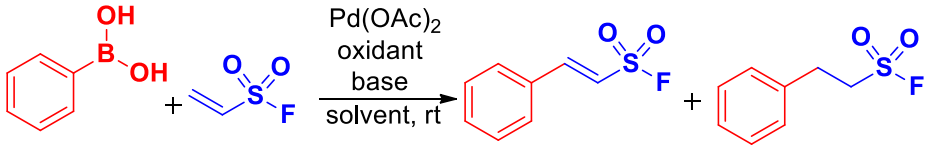
Next, we investigated the influence of various bases on the reaction yield. Using Cs_2CO_3 as a base there was no product formation observed, which could be due to hydrolysis of the sulfonyl fluoride, similar to our earlier findings on the cross-coupling of halo aryl sulfonyl fluorides.[4] The organic bases (DIPEA, TEA) did not provide any further improvement of yield (**Table 1, entries 3 & 4**). However, in the case of LiOAc as a base there was an improved reaction yield. Interestingly, reaction conditions using 10 mol % $Pd(OAc)_2$, 2.0 equiv. of $Cu(OAc)_2$, and 1.0 equiv. of LiOAc in DMF at room temperature exclusively gave the alkenyl product in 58% yield (**Table 1, entry 5**) along with a minor amount of the conjugate addition product. Conjugate addition has been reported by several other research groups for various other α, β-unsaturated cyclic/acyclic carbonyl systems.[2, 33-37]

To avoid the undesired homocoupling and conjugate addition, we slowly added the aryl boronic acid to the reaction mixture over a period of ~1h; thereby, we could avoid the homocoupling and observed a small improvement in the yield. Still, a small amount of conjugate addition product was observed under these conditions.

Finally, to achieve the optimized reaction conditions we explored various solvents {CH_3CN, toluene, THF, DCE and H_2O}. Polar aprotic solvents (CH_3CN, THF) gave moderate to good yields with minimum, or no, conjugate product formation (**Table 1, entries 6 & 7**). This suggested that nitrogen- and oxygen- containing solvents could act as ligands that stabilize the palladium coordination complex in the transition state[38, 39] and promote/switch the oxidative addition over to conjugate addition. The use of chlorinated non-polar aprotic solvent such as DCE resulted in an almost equal amount of the oxidative addition and conjugate addition products (**Table 1, entry 8**). Again, this could be due to the absence of coordinating heteroatoms (O and N)

in this solvent. This hypothesis was further supported from observations in non-polar aprotic solvent, *i.e.* toluene, where a conjugate addition product was observed as the major product; lower yields were also seen in toluene due to poor solubility of the starting materials (aryl boronic acid, LiOAc) in this solvent (**Table 1, entry 9**). In contrast to our previous report on cross-coupling reactions,[4] water as reaction solvent drastically decreased the reaction yield (**Table 1, entry 10**). Only trace amount of product formation was observed with some other byproducts, as well as small amounts of unreacted starting material; most likely, the super Michael acceptor ethenesulfonyl fluoride reacts with water under these conditions.[17]

Table 1: Optimization of reaction conditions[a]



2 **3** **4a** **5a**

Entry	Oxidant	Base	Solvent	Yield[b]/ %	Ratio[c] (4a:5a)
1	O_2	LiOAc	DMF	9.9	100:0
2	$Cu(OAc)_2$	DIPEA	DMF	26.5	100:0
3	$Cu(OAc)_2$	TEA	DMF	12	100:0
4	$Cu(OAc)_2$	Cs_2CO_3	DMF	NR	-
5	$Cu(OAc)_2$	LiOAc	DMF	58	95:5
6	$Cu(OAc)_2$	LiOAc	CH_3CN	28	92:8
7	$Cu(OAc)_2$	LiOAc	THF	77	100:0
8	$Cu(OAc)_2$	LiOAc	DCE	16.8	59:41
9	$Cu(OAc)_2$	LiOAc	toluene	9.5	31:69
10	$Cu(OAc)_2$	LiOAc	H_2O	TRACE	27:73

[a]**Reaction conditions:** Boronic acid (1.0 equiv.), ethenesulfonyl fluoride (3.0 equiv.), $Pd(OAc)_2$ (10 mol %), base (1.2 equiv.), oxidant (2.0 equiv. for $Cu(OAc)_2$) under dry conditions in 4.0 mL of solvent. [b]Isolated yield of **4a**. [c]Percentages based on GC/MS analysis of the crude reaction mixture (**4a** & **5a**).

With the optimized conditions in hand (10 mol % $Pd(OAc)_2$, 2.0 equiv. of $Cu(OAc)_2$, and 1.0 equiv. of LiOAc in THF at room temperature) we next investigated the substrate scope of the reaction using various substituted aryl boronic acids and ethenesulfonyl fluoride as a coupling partner (**Figure 10**). Reaction with simple phenyl

boronic acids proceeded smoothly in oxidative boron-Heck cross-coupling, without any conjugated addition, offering product **4a** in 77% yield. The electron-withdrawing groups (EWGs) (NO_2 and Br) offering products **4b**, **4c**, **4d**, **4e**, and **4f** in moderate to good yields without any conjugate addition product. However, substrates with electron-donating groups (EDGs), *i.e.* yielding products **4g** and **4h** in 48% and 43% yield respectively, gave a small amount of conjugate addition (<1%) byproduct. Steric effects did not seem to significantly influence the reaction, as substrates with 2-OMe, 2,6-di-OMe, and 2-OMe-5-chloro groups offered the corresponding products in moderate yields. Bicyclic (naphthalene; **4l** and **4m** in 55% and 55% yield) and heterocyclic (thiophene **4n**, 41% yield; Indole **4o**, 65%) boronic acids gave only small amounts of conjugate addition product along with oxidative boron-Heck product. We also attempted the same reaction conditions for heterocyclic boronic acids (*i.e.* quinazoline and pyridine), but these substrates did not offer any product, presumably due to complexation of the palladium with the nitrogen atoms in these substrates. Similarly, 2-NO_2 phenylboronic acid failed to give the respective product. In summary, the reported methodology offers acceptable yields of aryl ethenesulfonyl fluorides through an operationally simple oxidative Heck reaction using widely accessible boronic acids and ethenesulfonyl fluoride as reagents. The limitation in yields was due to unwanted deboronation of the aryl boronic acids, which was confirmed by GC-MS and previously reported in the literature.[40-42]

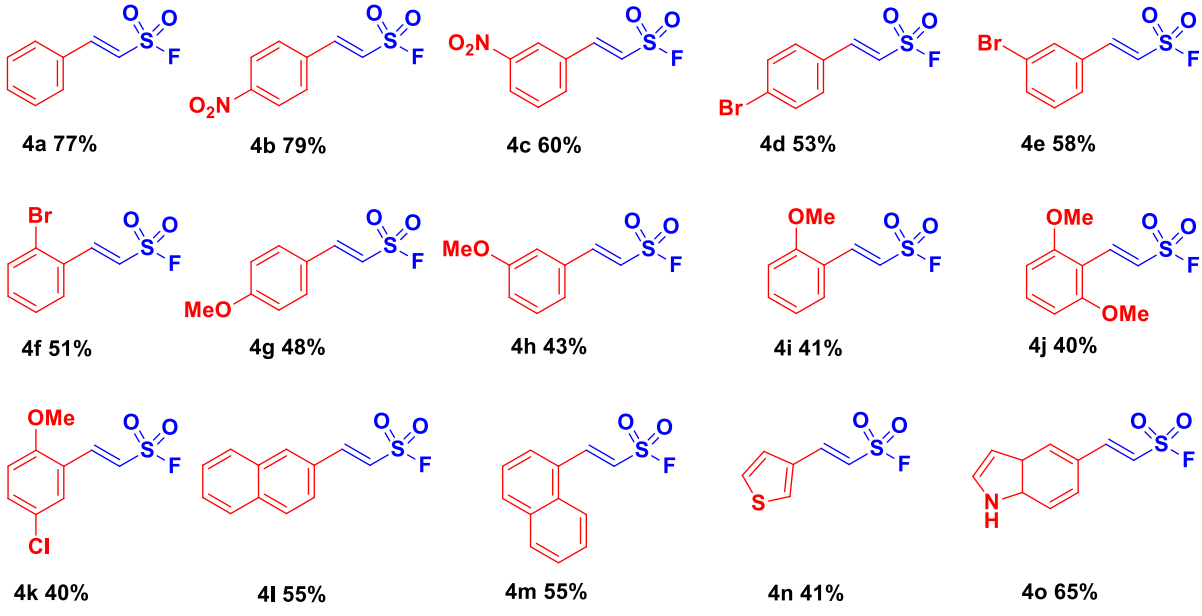
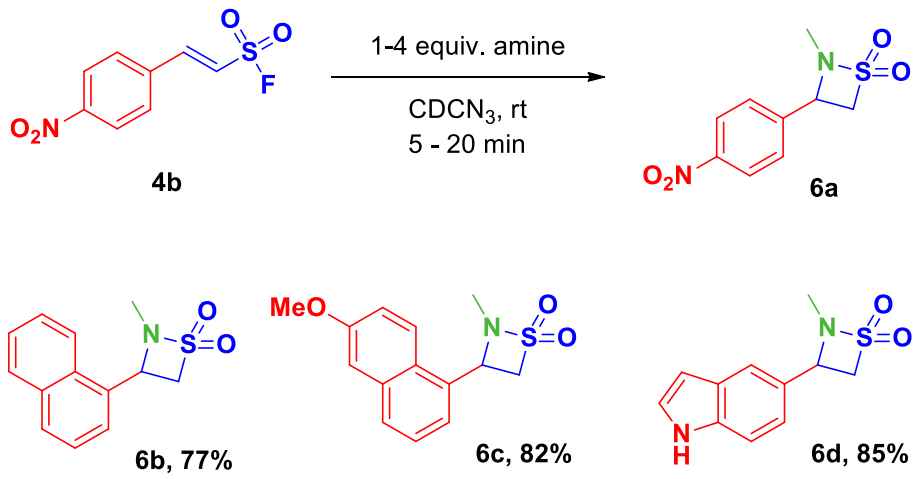


Figure 10: Substrate scope for the synthesis of aryl substituted ethenesulfonyl fluorides using oxidative Heck coupling of boronic acids and ethenesulfonyl fluoride (ESF)

In order to further demonstrate the synthetic potential of the disclosed methodology and explore the dual warhead concept of the *β*-aryl ethenesulfonyl fluorides, the addition of primary amines was investigated. The concurrent manuscript by Sharpless and co-workers[21] describe the selective conjugate addition of secondary

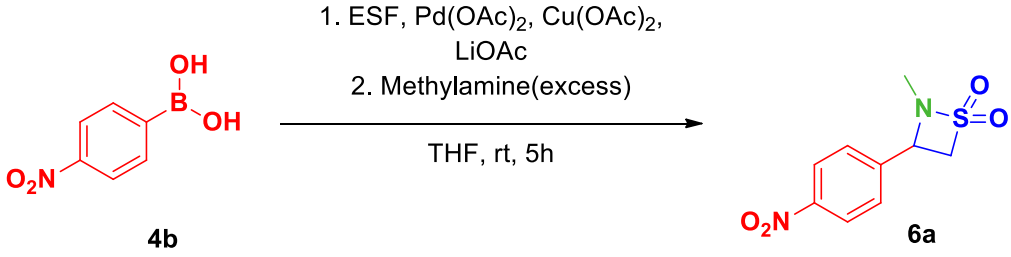
amines to the *β*-aryl ethenesulfonyl fluoride products without affecting the S–F bond, while Liskamp and co-workers[14] described an unexpected *β*-sultam formation in the presence of excess primary amines for their *β*-aliphatic ethenesulfonyl fluoride reagents. We initiated our investigation using NMR spectroscopy experiments by the addition of only 1.0 equiv. of isobutylamine to **4b**; under these conditions no reaction occurred after 5 minutes. Keeping the reaction mixture overnight led to 50% conversion to the corresponding *β*-sultam **6a**; notably, no trace of the corresponding Michael addition product could be detected in the sample. In the next experiment, we added aliquots (0.1 equiv.) of the amine sequentially to the NMR tube already containing 1.0 equiv. of isobutylamine and **4b**. We observed an increased formation of *β*-sultam **6a** until a total of 2.5 equiv. of amine had been added to reach 100% conversion to the *β*-sultam over 20 minutes. A separate experiment in which 4.0 equiv. of the amine was directly added to **4b** led to 100% conversion to the *β*-sultam in 2 minutes.



Scheme 13: Synthesis of *β*-sultams

We also probed the influence of DBU to see if this changed reactivity towards the S–F bond, or catalyzed the Michael reaction; addition of 1.0 equiv. of isobutylamine to **4b** in the presence of 0.1–0.5 equiv. of DBU led to slow formation of the *β*-sultam. With these results in hand, we investigated the scope of the *β*-sultam formation using excess methylamine in THF (See SI on the attached CD for details). The transformation worked well for a range of aryl ethenesulfonyl fluorides containing both electron-donating and -withdrawing groups, *i.e.* producing *β*-sultams **6b**-**6d** (**Scheme 13**). It is anticipated that the *β*-sultam forms *via* a Michael addition that in a concerted reaction expels F^- and forms a sulfene intermediate, to which the amine adds intramolecularly; substrates with EWGs appear to react faster than those with EDGs. Finally, we developed this method as a one-pot procedure. After completion of the oxidative boron-Heck reaction between the boronic acid and ethenesulfonyl fluoride, we directly added excess of methylamine to the reaction mixture

and stirred for another 5 minutes. This gave the corresponding *β*-sultam in high yield after column chromatography (**Scheme 14**).



Scheme 14: One pot-click synthesis of *β*-sultams

Conclusion

In summary, we have developed a facile synthetic method to access substituted *β*-aryl ethenesulfonyl fluorides using an oxidative boron-Heck cross-coupling reaction that proceeds under mild reaction conditions with moderate to good yields. The reported method is complementary to previously reported procedures and utilizes boronic acids, a class of starting material that has widespread commercial availability. The obtained aryl substituted ethenesulfonyl fluorides represent a "dual warhead" with two electrophilic sites that has found use as covalent enzyme inhibitors and as synthetic reagents. We also demonstrate that *β*-sultams, another class of covalent enzyme inhibitors, may be obtained through a one-pot procedure in which an excess of primary amine is added to the reaction mixture before workup.

Associated Content

Supporting Information

Experimental procedures and full characterization data (^{1}H, ^{19}F, ^{13}C and GC-MS) with copies of spectra for all the compounds can be found on the accompanying CD to this thesis.

AUTHOR INFORMATION

Corresponding Author

*E-mail: per.arvidsson@scilifelab.se

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work is based on the research supported in part by the National Research Foundation of South Africa for the Grant 87706. We are also grateful to Claude Leon foundation for postdoctoral fellowship to PKC, UKZN

postdoctoral fellowship to SKA and master fellowship to KBG, and to Dr. Lisa D. Haigh at Imperial College London for swift assistance with HRMS.

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CHAPTER 3

A Potentially New Synthetic Route to Naratriptan

Introduction

One of the most common and chronic neurological disorders, which affects 1-2 % of the general population, is migraines.[1] It is known to be three times more common in women[2], it is also the 19th most disabling disease[3] and third most prevalent disease in the world.[4] Often characterized by throbbing and unilateral pain and in severe cases, includes nausea and vomiting.[3] In many instances it still remains misdiagnosed and undertreated.[5, 6] A breakthrough in the treatment of migraines came about during the discovery of Sumatriptan (**Figure 11a**), an indole based drug,[7, 8] which later gave birth to a new family of compounds known as triptans. Triptans are tryptamine-based compounds and are known agonists for serotonin or 5-hydroxytryptamine (5-HT) receptors particularly 5-$HT_{1B/1D}$ receptors. There are several potential modes of action most of which include a constriction of the intercranial blood vessels, alleviating pain.[9] Triptans have several advantages over other treatments for migraines such as fewer side effects, selective pharmacology, simple pharmacokinetics and good efficacy.[3]

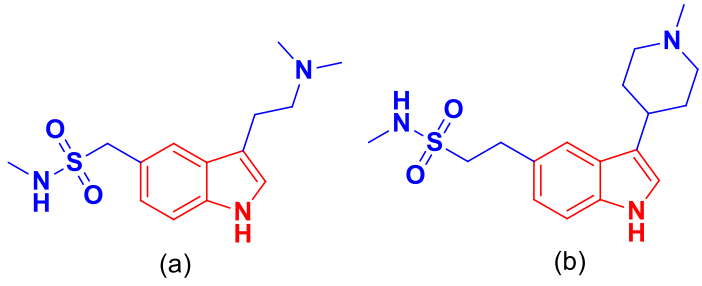
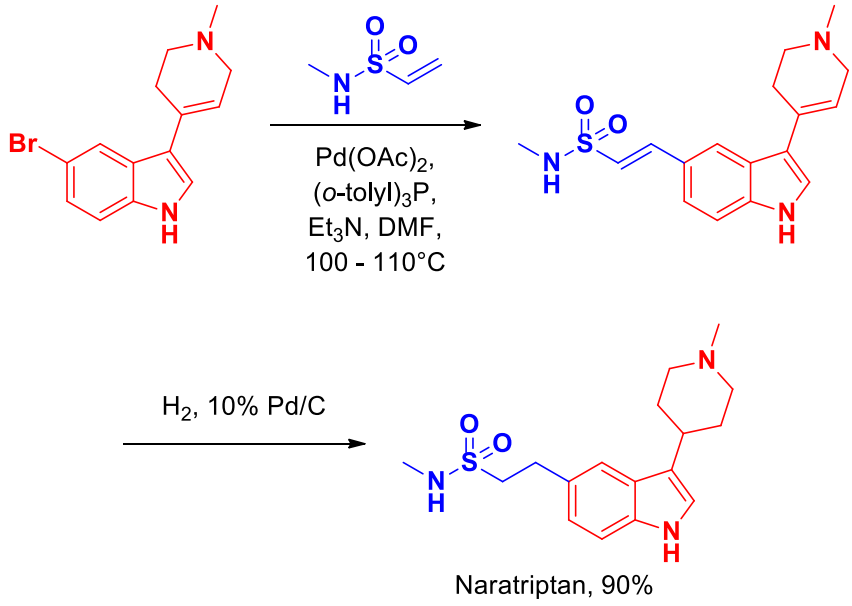


Figure 11: Structures of (a) Sumatriptan and (b) Naratriptan

There are several triptans now commercially available in the markets such as Rizatriptan, Eletriptan, Almotriptan, Zolmitriptan and Naratriptan, which differ in the sulfonamide moiety and the side chain on the indole. These triptans were developed as a means to counteract the pitfalls of Sumatriptan, such as poor efficacy and negative side effects on a patient's chest and throat.[10] Naratriptan (**Figure 11b**), in particular, offers several advantages over the parent Sumatriptan such as improved lipophilicity, bioavailability and a longer half-life. As a result, Naratriptan has fewer side effects, improved efficacy and a decrease in the re-occurrence of migraines after treatment.[10] Based on this, it is now regarded as one of the top selling heterocycle containing drugs,[11] which has increased the attention on the optimisation of its preparation.

There are several ways in which Naratriptan can be synthesized, which has been reported and patented. Early patents described a Mizoroki-Heck reaction between *N*-methylvinylsulfonamide and substituted

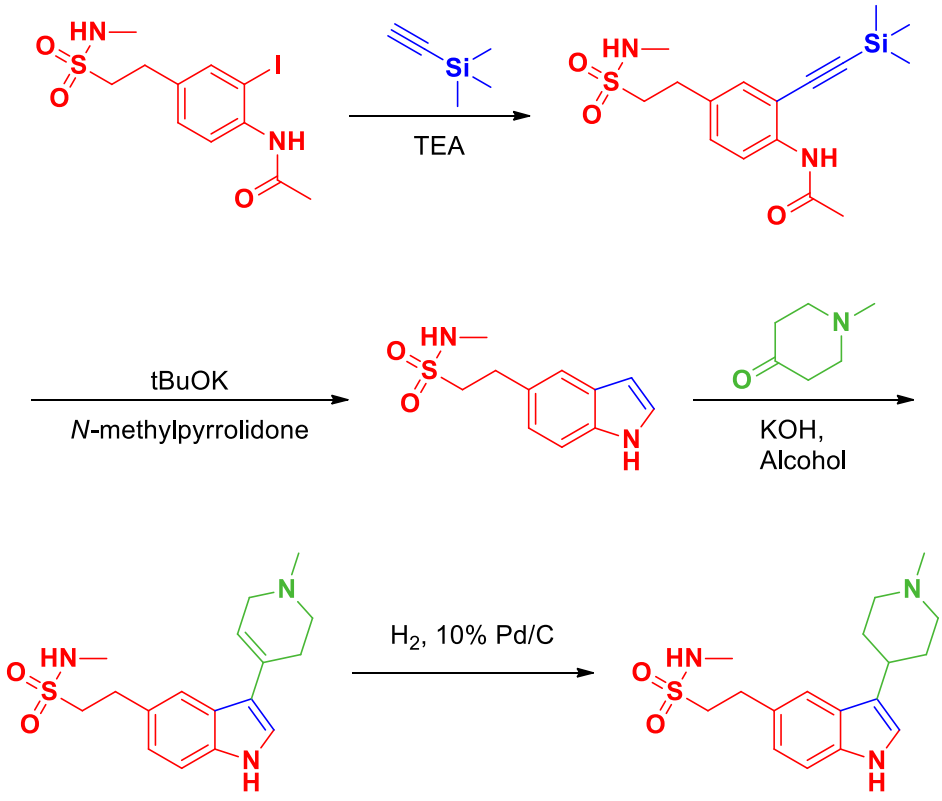
bromoindoles, followed by a hydrogenation as depicted in **Scheme 15**.[12-14] The use of *N*-methylvinylsulfonamide and bromoindoles proves difficult as it is not commercially available. László and co-workers developed two separate multi-step syntheses, involving alternate starting materials such as carbaldehydes[15] and vinyl sulfonic acids.[16] These new synthetic routes involved harsh and expensive chemicals such as $TiCl_4$ and sodium metal, and typically resulted in poor overall yields.



Scheme 15: Heck reaction used for the synthesis of Naratriptan[11, 17]

Research was then re-focused back to the Mizoroki-Heck reaction. Shashikumar and co-workers developed a simple one-pot method for the synthesis of the bromoindole derivative used in the original patents.[18] By means of a triethylsilane and acid reduction, the authors were able to obtain the indole derivative in high yields (>90%) and in high purity (>99%). Conversely, Venugopala and co-workers developed a simple method to synthesize *N*-benzyl-*N*-methyl ethenesulfonamide, an alternative to the *N*-methylvinylsulfonamide, in which the polymer properties were problematic.[19] The *N*-benzyl-*N*-methyl ethenesulfonamide is prepared from commercial products and is also obtained in high yields and purity (>95%). The authors then applied this new intermediate to the total synthesis of Naratriptan. While the overall yields were good, the synthetic route involved an additional Birch reduction for the deprotection of the sulfonamide.

The current patent for the synthesis of Naratriptan involves a reaction of sulfonamide with trimethyl silyl acetylene, as shown in **Scheme 16**.[20] This is followed by a one-pot desilylation, deprotection and cyclization which yields the indole intermediate. A final Aldol condensation using *N*-methyl-4-piperidone yields the desired Naratriptan. The main downfall for this synthetic route is that the starting sulfonamide is not commercially available and involves several steps to prepare.

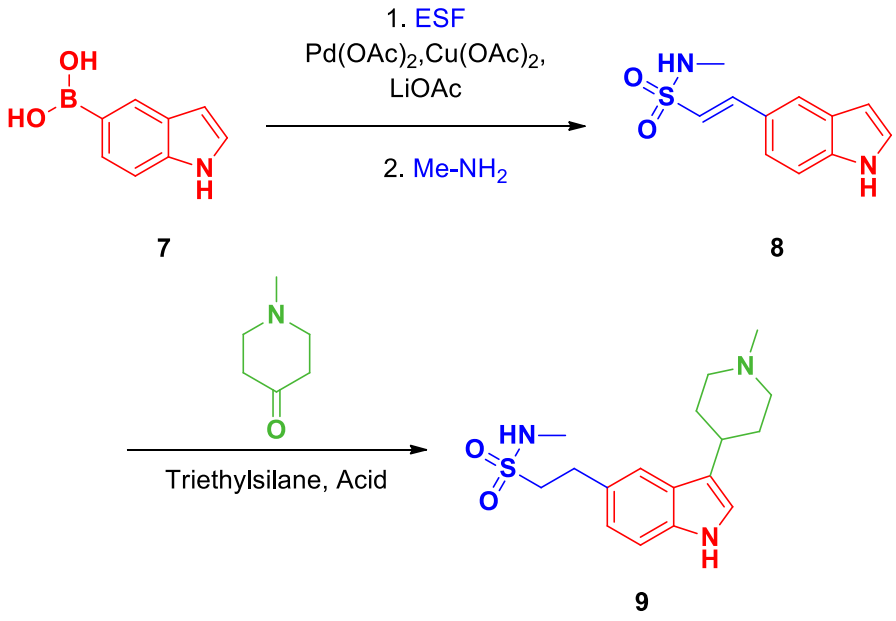


Scheme 16: Current synthesis of Naratriptan[20]

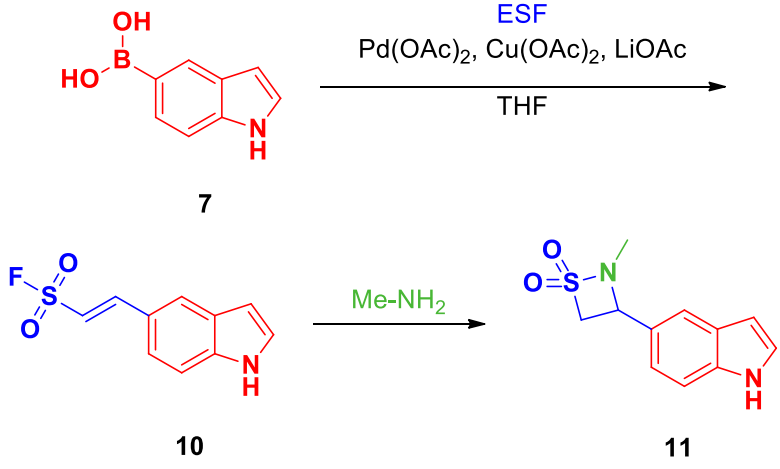
Thus, our main aim was to develop a new synthetic route toward the synthesis of Naratriptan which would make use of commercially available materials. Since we had previously reported an oxidative Heck reaction (**Chapter 2**), which employed the use of eco-friendly boronic acids, thus we envisaged to apply this methodology toward the total synthesis of Naratriptan.

Results and Discussion

We initially proposed the synthesis towards Naratriptan as shown in **Scheme 17**, however based on results obtained in **Chapter 2**, it was found that the addition of methylamine results in the formation of a *β*-sultam (*e.g.* **11**). Thus, we began by carrying out the reported oxidative Heck reaction with the commercially available 5-indolylboronic acid (**7**) and ESF which was reacted with $Pd(OAc)_2$, $Cu(OAc)_2$, and LiOAc in THF. Upon completion and purification, **10** was reacted with excess methylamine in ethyl acetate, which resulted in the formation of 1-(4,5'-indolyl-1,1-dioxido-1,2-thiazetidin-2-yl)methyl (**11**), as shown in **Scheme 18**.



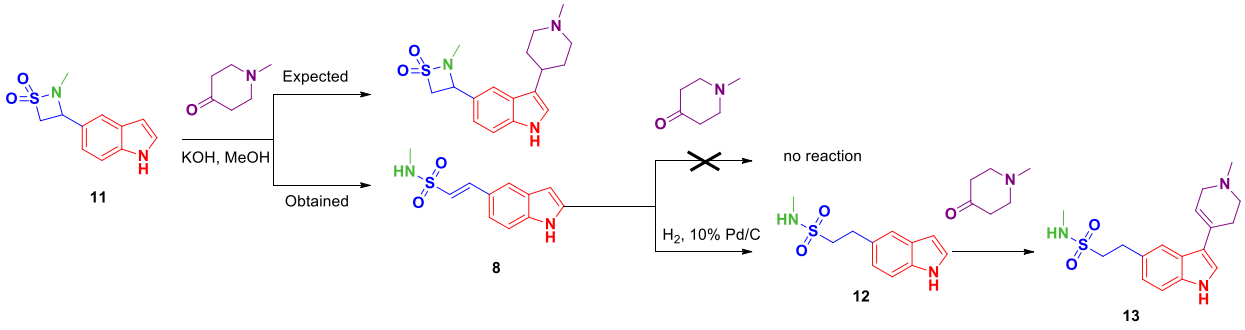
Scheme 17: Initial proposed synthesis of Naratriptan



Scheme 18: Synthesis of *β*-sultam

In order to attach the piperidine ring to **11**, an Aldol condensation reaction was attempted using the ketone under basic conditions (KOH in MeOH, shown in **Scheme 19**). It was observed, however, that the basic conditions resulted in the ring opening of the *β*-sultam **11** producing the vinyl sulfonamide **8**. Ring opening reactions of *β*-sultams are known, however they typically proceed *via* a nucleophilic addition resulting in the formation of a *β*-aminosulfonyl derivative.[21, 22] This is the first account of a ring opening reaction of *β*-sultams which results in the formation of a vinyl sulfonamide, which likely occurs *via* an E1cB mechanism.[23] The use of a stronger base *viz.* KOtBu in THF under reflux, resulted in the complete conversion of the *β*-sultam to the vinyl sulfonamide, however isolated yields were low due to the reactivity of **8**.[24] Future prospects should involve the optimisation of this step.

After obtaining **8**, the compound was then subjected to another Aldol condition but the desired product was not obtained. It was hypothesized that the presence of the additional double bond adjacent to the sulfonamide prevents the selective addition of the piperidine onto the indole ring, as reported methods typically use the saturated analogue **12**.[25] Thus, we proposed to first hydrogenate **8** to obtain **12**, and the carry out the Aldol reaction shown in **Scheme 19**. Once completed, product **13** can be subjected to hydrogenation to yield Naratriptan **3**.



Scheme 19: Attempted synthetic steps toward the synthesis of Naratriptan

Conclusion

The oxidative Heck chemistry developed in **Chapter 2** was investigated for a key role in the synthesis of Naratriptan, a highly effective drug used for the treatment of migraines. This methodology proved effective in attaching ESF to the core indole scaffold as desired. However, subsequent steps to prepare the target Naratriptan were met with some challenges. Treatment of the β-sultam with base resulted in an unexpected, novel ring opening reaction (E1cB) to form a vinyl sulfonamide. However, this species was observed to be unreactive in the Aldol condensation to add the piperidine unit. It was concluded that as a future prospect the vinyl sulfonamides be further reduced before it can be applied to the synthesis of Naratriptan.

Experimental Details

General Information

All commercially available reagents were purchased from Aldrich and Merck, and used as received. Solvents were of reagent grade and dried prior to use using standard drying procedures. Thin-layer chromatography (TLC) was done using pre-coated silica gel 60 F_{254} plates. Column chromatography was done using neutral alumina. All NMR spectra were recorded on Bruker Advance III 400 MHz instrument in $CDCl_3$ at room temperature. The residual signal of $CDCl_3$ was used as a reference and all signals were expressed in ppm relative to TMS. Coupling constants are reported in Hz.

Synthesis and Characterization

[*E*]-2-(1H-Indol-5-yl)ethenesulfonyl fluoride (10): A sealed tube under nitrogen atmosphere was charged with ethenesulfonyl fluoride (93 µL, 1.12 mmol), $Pd(OAc)_2$ (8.3 mg, 10 mol %), $Cu(OAc)_2$ (135 mg, 0.74 mmol), LiOAc (29.5 mg, 0.44 mmol) and 2 mL of dry THF. The 5-Indolylboronic acid (**7**) (60 mg, 0.37 mmol) was dissolved in 1 mL of dry THF and added to the reaction mixture dropwise using a syringe over ~1h. Upon completion of the addition of **7**, the reaction was stirred at room temperature for 3h and monitored by TLC. Once complete, the reaction mixture was filtered through Celite. The filtrate was concentrated under vacuum and purified through neutral alumina column chromatography which gave the product **10** (53.9 mg, 65%) as a brown solid. R_f = 0.50 (25 % EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (1H, s, NH), 7.85 (1H, d, *J* = 15.4 Hz), 7.77 (1H, s), 7.39-7.31 (2H, m), 7.22 (1H, t), 6.71 (1H, dd, *J* =15.4, 2.4 Hz), 6.57 (1H, s) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.8 (d, $^3J_{CF}$ = 2.2 Hz), 138.0, 128.2, 124.3, 123.0, 121.9, 113.7 (d, $^2J_{CF}$ = 27.0 Hz), 112.1, 104.0 ppm. ^{19}F NMR: δ 63.2 ppm.

1-(4,5'-Indolyl-1,1-dioxido-1,2-thiazetidin-2-yl)methyl (11): A sealed 50 mL round bottom flask was charged with **10** (220 mg, 0.98 mmol) and excess methylamine solution in 20 mL of EtOAc. The reaction mixture was stirred at room temperature for 20 minutes. Upon completion, the reaction mixture was concentrated under vacuum and purified through neutral alumina column chromatography which gave the compound **11** (190 mg, 82 %) as a light brown solid. R_f = 0.5 (28 % EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (1H, s, NH), 7.66 (1H, s), 7.37 (1H, d, *J* =8.4 Hz), 7.24 (1H, dd, *J* =8.4 Hz), 7.20 (1H, t, *J* = 2.84 Hz), 6.51-6.50 (1H, m), 4.34 (1H, dd, *J* = 12.1, 7.5 Hz), 4.20 (1H, t, *J* = 7.4 Hz), 4.00 (1H, dd, *J* = 12.1, 6.2 Hz), 2.63 (3H, s) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.0, 128.0, 127.4, 125.4, 120.2, 119.5, 111.8, 102.7, 66.5, 52.7, 30.2 ppm.

[*E*]-2-(1H-indol-5-yl)-*N*-methylethenesulfonamide (8): A 100 mL round bottom flask was charged with **11** (200 mg, 0.85 mmol) and potassium tert-butoxide (191 mg, 1.7 mmol) in 10 mL of dry THF. The reaction was refluxed for 22h and monitored by TLC. Upon completion, water (10 mL) was added and the mixture was extracted using EtOAc (3 x 10 mL). The organic layer was dried with $MgSO_4$, evaporated and purified by neutral alumina column chromatography which gave the compound **8** (20 mg, 10 %) as an off-white solid. R_f = 0.5 (45 % EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.27 (1H, s, NH), 7.72 (1H, s), 7.56 (1H, d, *J* = 15.3 Hz), 7.35-7.28 (2H, m), 7.20 (1H, d, *J* = 3 Hz), 6.55 (1H, d, *J* = 15.3 Hz), 6.53 (1H, t), 4.10 (1H, d, NH, *J* = 5.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.4, 137.2, 128.2, 125.6, 124.6, 122.7, 121.6, 120.3, 111.7, 103.6, 29.4 (d, *J* = 53 Hz) ppm.

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CHAPTER 4

Organocatalytic transformations of ethenesulfonyl fluoride

Abstract

There are several modes of action in organocatalysis, but these have yet to be applied to ESF. Herein, we report the application of ESF to various Michael reactions by employing different organocatalysts with varying modes of action. It was found that a reaction with ESF and cyclic β-ketoesters in the presence of a chiral thiourea hydrogen bond catalyst, resulted in the best reactivity. Determination of the enantioselectivity of the reaction was successful by measuring the optical rotation of the product. This preliminary study has now opened the door for the use of ethenesulfonyl fluoride as a substrate in organocatalysis.

Introduction

As described in the introductory chapter, the use of small and chiral organic molecules as catalysts is fast becoming a vital tool in chemical synthesis. These molecules present several advantages that have resulted in its application in the total synthesis of many biologically important molecules.[1] The versatility of organocatalysts are predominantly due to the various interactions that can occur between the substrate and catalyst or "modes of action." These interactions are divided into covalent and non-covalent interactions (**Figure 12**). Covalent interactions refer to a covalent bond that forms between the substrate and the catalyst. The formation of new bonds constrains the reactants into specific orientations leading to a stereoselective reaction, if a chiral catalyst is used. The covalent mode of action can be further divided into three groups *viz.* enamine, iminium and singly occupied molecular orbital (SOMO).

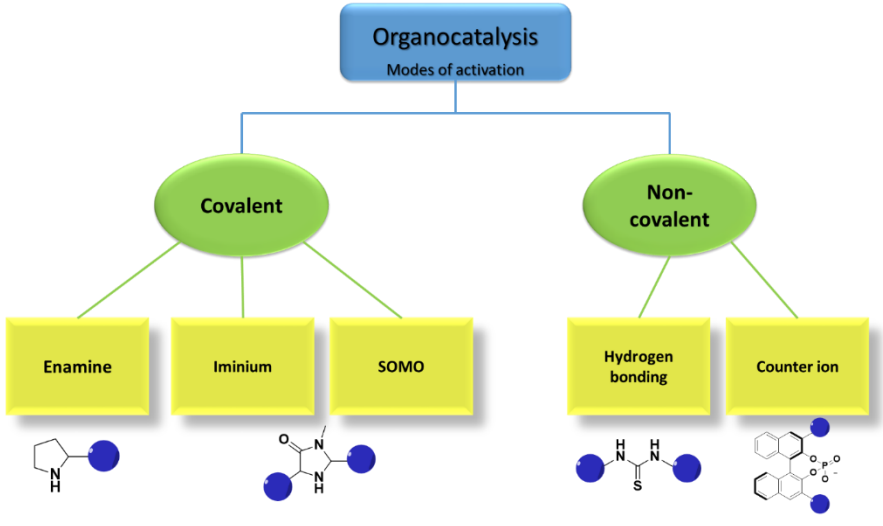


Figure 12: Typical modes of activation in organocatalysis[1, 2]

The enamine mechanism was one of the very first organocatalytic mechanisms employed, where proline was used to catalyze an enantioselective intramolecular Aldol condensation.[3] It is referred to as enamine catalysis as the proline based catalyst participates in the formation of an enamine with the ketone or aldehyde substrate, and is thus typically used for Mannich,[4] and Michael type reactions.[5] The enamine mechanism is also often referred to as highest occupied molecular orbital (HOMO) activation whereby the formation of the enamine increases the nucleophilicity of the substrate by raising the energy of the HOMO and allowing the reaction to proceed faster.[6] Conversely, for the iminium mode of action, the aldehyde or ketone substrate forms an iminium ion with the catalyst *e.g.* an imidazolidinone. This results in the increase of electrophilicity of the substrate and a decrease in the energy of the lowest unoccupied molecular orbital (LUMO), thus it is referred to as LUMO activating. This mechanism is often employed in Diels-Alder type reactions.[7]

The imidazolidinone catalyst can also be employed in a third covalent mode of action known as SOMO. In this case, the substrates form an enamine with the catalyst before further undergoing a single electron oxidation, which creates the highly reactive SOMO. This allows for various functionalizations at the α-carbon on aldehydes.[3]

The second mode of action within organocatalysis that can occur is non-covalent, whereby the substrate interacts with the catalyst through weak interactions through space *i.e. via* hydrogen bonding or by ionic interactions. The hydrogen bonding catalysts can increase the nucleophilicity of the substrate, which was demonstrated by the dual activation of Takemoto's catalyst (**Figure 13**).[8] The presence of two hydrogens not only further increases activation but also aids in the control of the stereoselectivity of the reaction by restricting the molecules into specific orientations. Hydrogen bonding catalysts have thus also been employed in many asymmetric Michael and Mannich type reactions.[9]

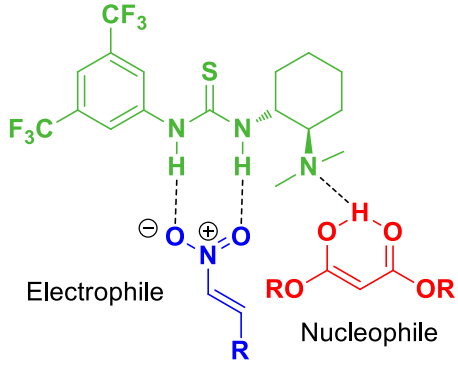


Figure 13: Takemoto's catalyst showing dual activation of electrophile and nucleophile[8]

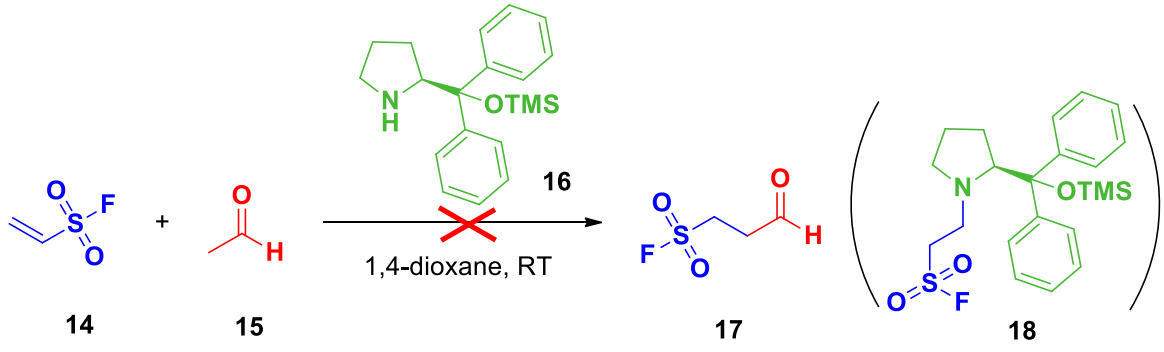
The second non-covalent interaction is counter ion, in this case, a catalyst anion is often generated using a chiral salt, which forms an ion-pair with a cationic substrate.[10, 11] Apart from the ion-pair interaction increasing the electrophilicity of the substrate, the presence of the enantiomerically pure anion results in an

enantioselective reaction. This mode of activation can be applied to modified Mannich reactions such as Pictet-Spengler cyclizations.[12]

With the vast modes of action available, we wished to apply some of these modes to the title compound (ESF), which is a novel substrate in organocatalysis. Based on the ability of ESF to act as connector molecule,[13] as discussed in earlier chapters, we believed the use of ESF in enantioselective reactions will result in chiral intermediates, which could be applied to the total synthesis of biologically active compounds.

Results and Discussion

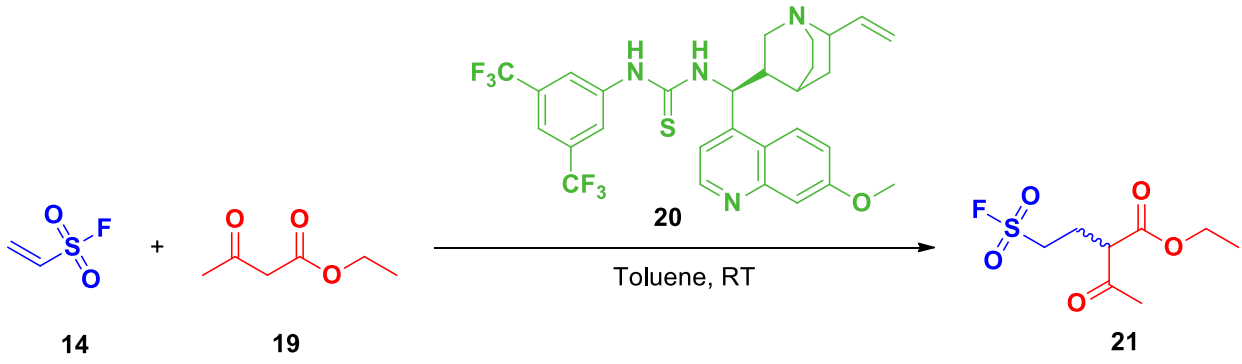
A comprehensive study comparing ESF to other common, good Michael acceptors revealed it to be far superior,[14] hence we wished to use the ESF in a number of Michael reactions by employing the different modes of action. We began our initial investigation by carrying out a Michael reaction *via* the enamine mode where a proline based, diphenylprolinol silyl ether (**16**) was used as the catalyst (**Scheme 20**). The reaction was monitored by TLC and it was found that the ESF (**14**) had been completely consumed in one hour. The crude mixture was then analysed by means of GC-MS but the mass of the expected product **17** could not be detected. The crude mixture was further analysed by ^{1}H NMR and it was found that the ESF had reacted with the primary amine on the catalyst, resulting in product **18** in **Scheme 20**. This is a plausible result as it is known that ESF has a strong affinity to react and form bonds with primary and secondary amines.[13, 15] This effectively rules out the application of the remaining two covalent modes of action to ESF.



Scheme 20: Initial Michael reaction attempted on ESF[5]

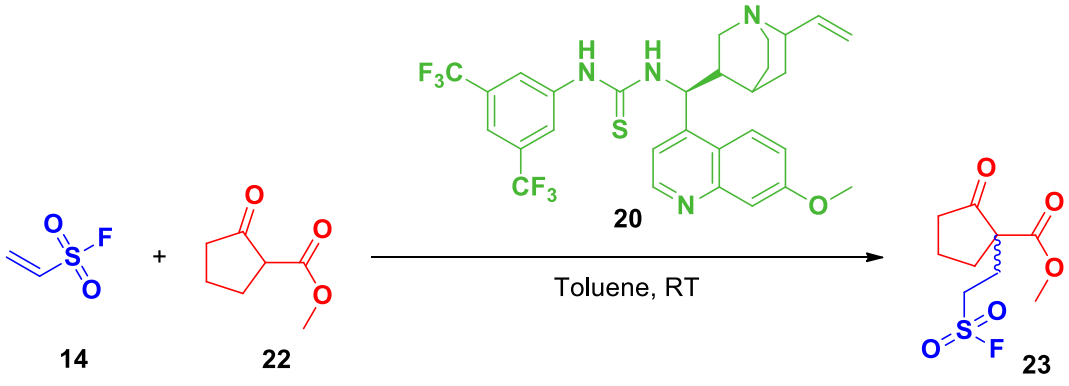
Next, we focused our attention on the non-covalent mode of action, specifically the hydrogen bonding mechanism. The ESF was reacted with a linear *β*-ketoester (**19**) in the presence of 10 mol % of the thiourea based catalyst (**20**) as shown in **Scheme 21**. A *β*-ketoester was chosen as these compounds are a popular substrate in organocatalysis, forming a simple synthon for many biological compounds.[16] To prevent any unwanted reactions, a catalyst with a tertiary amine was chosen. The reaction was monitored by means of GC-MS and after one hour it was found that the desired product had formed, however there was a significant

amount of starting material remaining. The reaction was further monitored over a period of two days and it was found that the amount of starting material did not decrease. This is likely due to catalyst deactivation.



Scheme 21: Reaction between ESF and a linear β-ketoester in the presence of a hydrogen bonding catalyst

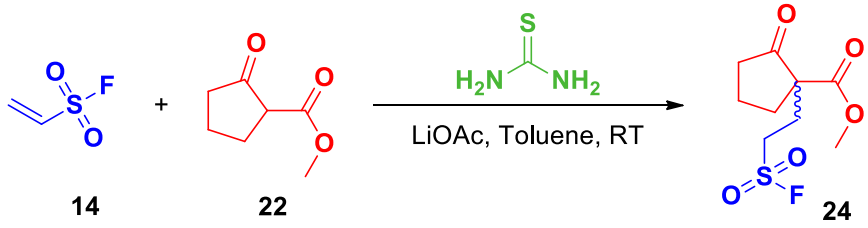
In an attempt to increase the reactivity, the linear *β*-ketoester was replaced with a cyclic analogue, as it is known that the cyclic variations are more reactive.[17] The same conditions were followed as above, however the cyclic methyl 2-oxocyclopentanecarboxylate (**22**) was used instead, as shown in **Scheme 22**. The reaction was again monitored by GC-MS and after three hours, it was found that the reaction had completed, with no starting material remaining. Product **23** was then purified by column chromatography and the structure confirmed by NMR. As a control, the reaction was repeated without the addition of the thiourea catalyst, and it was found, after a period of two days, that no product had formed. This result confirms the dependence of the reaction on the catalyst.



Scheme 22: Reaction between ESF and a cyclic *β*-ketoester

Product **23** contains a chiral centre and thus can form enantiomers. To determine if the presence of the chiral catalyst resulted in an enantioselective reaction, *i.e.* the formation of one of the enantiomer over the other, synthesis of the racemate was necessary. The formation of the racemate was carried out by reacting **14** and **22** in the presence of a non-chiral environment containing 50 mol % of thiourea and 50 mol % of LiOAc (**Scheme 23**). The base, LiOAc, is used to abstract the acidic proton on **22** to initiate the reaction. We began

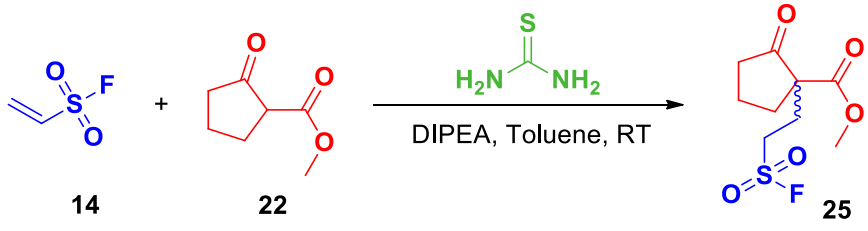
the reaction with the inorganic base, LiOAc, based on previous studies which can be found in **Chapter 2**, which indicate that this base will not decompose **14**.



14 **22** **24**

Scheme 23: Formation of racemate using LiOAc as base

By monitoring by GC-MS, it was found that after one hour, the desired product (**24**) had formed but the reaction was incomplete. The reaction was then refluxed for three hours but the amount of starting material did not diminish. The same result was observed when the reaction was left to reflux overnight. It is important for the reaction to go to completion as the starting material **22** and the product **24** have very similar properties, which makes separation and purification difficult. In an attempt to resolve this, the inorganic base was replaced with a more soluble organic base *viz.* DIPEA and the reaction was carried out as shown in **Scheme 24**. This proved successful, as after four hours the reaction had completed and the product was purified *via* column chromatography.



14 **22** **25**

Scheme 24: Formation of racemate using DIPEA as base

With the product in hand, we then began the chiral HPLC analysis of the racemate to determine the enantioselectivity of the chiral catalyzed reactions. Typically, a racemate subjected to a chiral column, will display two peaks of equal area in the HPLC spectrum, as shown in **Figure 14**. The product **25** was first run in a mobile phase of 0.5 % *iso*-propanol in hexane, which resulted in the spectrum as shown in **Figure 15**. However, any alteration to the mobile phase composition and flowrate did not improve the separation. Based on this result, we then ran the product obtained from the chiral catalyzed reaction depicted in **Scheme 22**. To our surprise, the HPLC spectrum was an exact match to that of the racemate indicating that the reaction did not proceed enantioselectively.

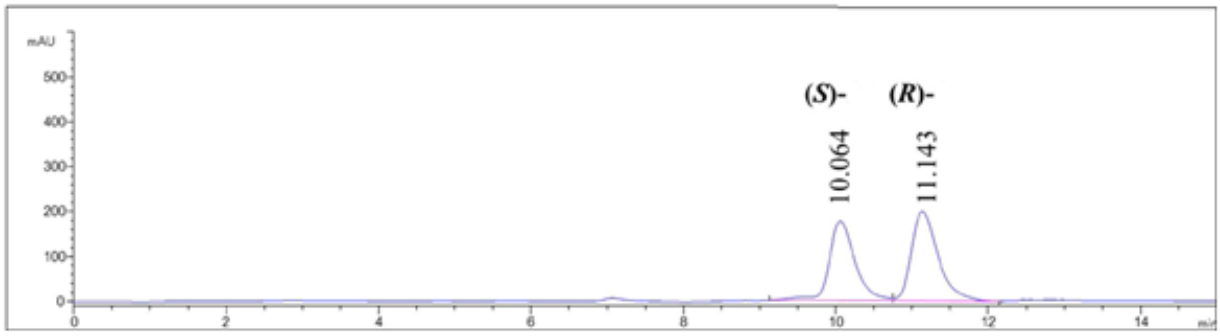


Figure 14: Typical HPLC spectrum for a racemate[18]

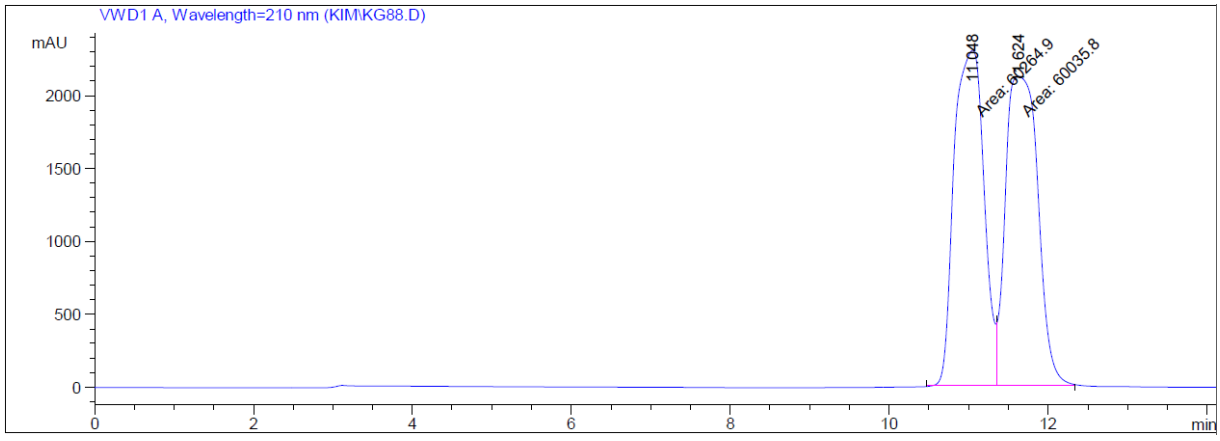
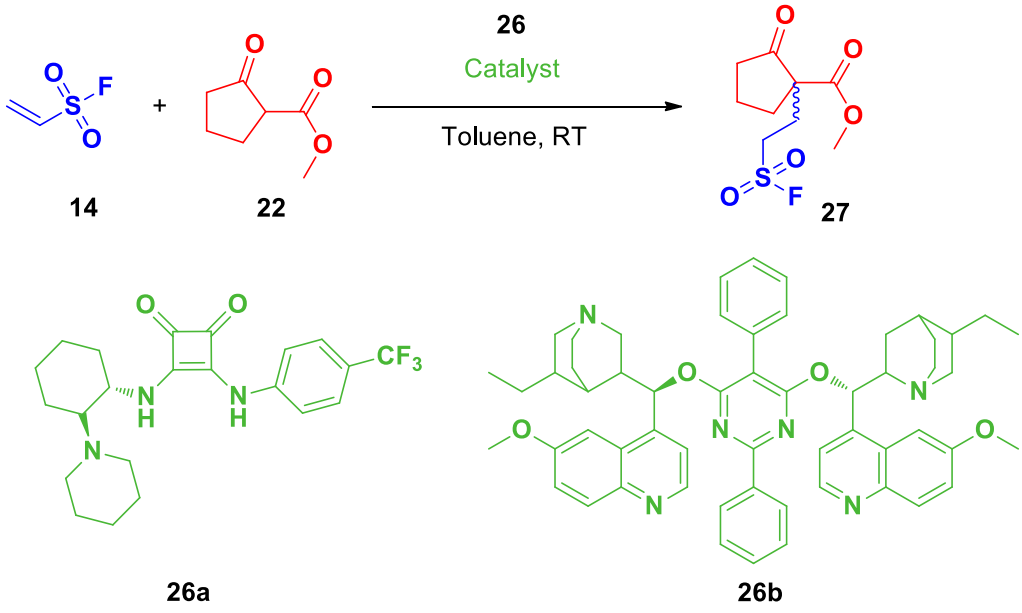


Figure 15: HPLC spectrum of racemic product 12

The reaction in **Scheme 22** was then repeated using two other hydrogen bond chiral catalysts, shown in **Scheme 25**, in an effort to obtain an enantioselective reaction. We first employed a squaramide catalyst (**26a**), which are known to work analogously to thiourea catalysts.[19] Monitored by GC-MS it was found that after 24 hours the desired product (**27**) had formed. However, this catalyst showed poor reactivity, which has been observed before, with some reactions requiring days to complete at room temperature.[20, 21] After a period of five days, the reaction had not reached completion, thus we employed the third hydrogen bonding catalyst (**26b**). This offered better reactivity, with the reaction reaching completion in 18 hours. The product **27** was purified *via* column chromatography and analysed by chiral HPLC.



Scheme 25: Use of different chiral hydrogen bonding catalysts

In all chiral HPLC runs, hexane was used for the sample preparation. It was found that the product obtained when catalyst **26a** was employed began to precipitate out of the solvent. Thus, we changed the solvent system and used methanol for the sample preparation and HPLC runs. With the change of solvent, a dominant peak was observed in the HPLC spectrum (**Figure 16**) for product **27**, which typically occurs when the reaction proceeds enantioselectively and one enantiomer forms in excess over the other. To confirm this result, the racemic product (**Scheme 24**) was analysed again *via* HPLC using methanol, however the same spectrum as in **Figure 16** was observed. This result proved to be rather peculiar as the racemate in any solvent should have appeared as two equal peaks, as stated before. To prove this, a crystal of the racemate (**Scheme 24**) was then grown, the ORTEP diagram of which is shown in **Figure 17**, using hexane and when analysed it confirmed that it was indeed the racemate, the details of this can be found in **Chapter 5**.

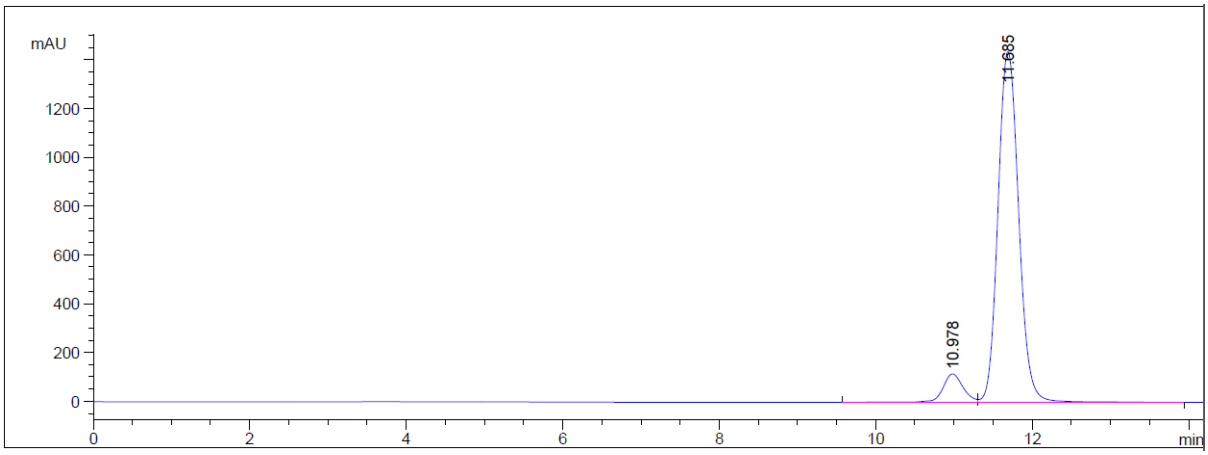


Figure 16: HPLC spectrum after change of solvent

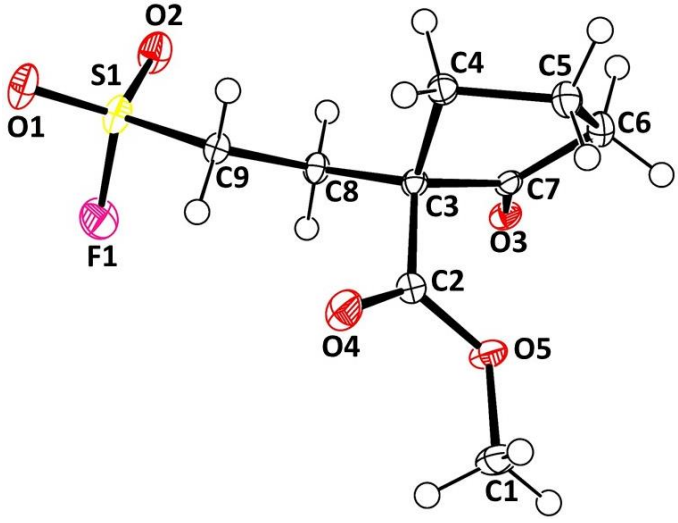


Figure 17: ORTEP diagram of compound **25** showing 50% probability thermal ellipsoids

This led to confusion as the change in solvent had resulted in a different spectrum, indicating that one enantiomer is more soluble in methanol than in hexane, which is unlikely without the addition of a chiral additive.[22] Screening of different columns and solvent systems did not assist with understanding this solubility issue, which prevented us from determining if any of the hydrogen bond catalyzed reactions had proceeded enantioselectively. Thus, in a final attempt to prove this we looked at the specific rotation of the racemate (**Scheme 24**) and compared it with that of the products obtained in the chiral catalyzed reactions.

The ability of a molecule to rotate the plane of polarized light is an important criterion for the molecule to be recognized as chiral. This ability is measured and described by the specific rotation of the compound. For a racemic mixture the net rotation is zero while a chiral molecule would have either a positive or negative value.[23] The product **25** obtained from the racemic reaction was measured using a polarimeter and the expected value of zero was observed. The product **23** obtained from the reaction employing the thiourea

hydrogen bonding catalyst was measured and a value of -33.9 was seen. This indicates that there is a dominant enantiomer when the chiral thiourea catalyst was used.

Since we know the reaction proceeds enantioselectively, we propose to derivatize the products obtained in future such that it can be analysed on the chiral HPLC and the *ee* of the reaction can be determined. We also propose to expand the scope of ESF as a substrate in organocatalyzed reactions by further exploring its unique electrophilic nature.

Conclusion

In summary, we have applied ESF as a substrate for various organocatalyzed Michael reactions. Reactions with tertiary amine-based hydrogen bonding catalysts were successful, however attempts to determine if the reactions were enantioselective by means of chiral HPLC proved challenging. The use of different columns and solvent systems did not provide conclusive results, however the specific rotation of the products determined that the reaction proceeded enantioselectively. Hence, we believe we have established a new substrate for organocatalyzed reactions that should be pursued and expanded in the future.

Experimental Section

General

Reagents and solvents were purchased from Aldrich and Merck, and used as received. Thin-layer chromatography (TLC) was done using pre-coated silica gel 60 F_{254} plates. Column chromatography was done using silica gel (70–230 mesh). All NMR spectra were recorded on Bruker Advance III 400 MHz instrument in $CDCl_3$ at room temperature. The residual signal of $CDCl_3$ was used as a reference and all signals were expressed in ppm relative to TMS. Coupling constants are reported in Hz. Optical rotations were recorded on a Bellingham & Stanley ADP440+ Polarimeter. GC-MS analysis was carried out using a Shimadzu GC-2010 Plus gas chromatograph coupled with a Shimadzu QP2012 Ultra mass spectrometer and Shimadzu AOC-20i auto injector system. A SLB™ -5ms capillary column (30m x 0.25 mm) with hydrogen as the carrier gas and electron impact ionization (EI, 70 eV) was used.

Procedure for the synthesis of racemic methyl-1-(2-(fluorosulfonyl)ethyl)-2-oxocyclopentanecarboxylate (25)

A mixture of methyl 2-oxocyclopentane carboxylate (100 mg, 1 equiv.), thiourea (0.20 equiv.) and DIPEA (0.20 equiv.) was stirred in toluene (4 mL) at room temperature. To this, ethenesulfonyl fluoride (4 equiv.) was added. The reaction progress was monitored by GC-MS. Upon completion, the reaction mixture was diluted with DCM and passed through a small amount of silica. The solvent was removed under reduced pressure to afford the product as a colourless oil (80 %). R_f = 0.44 (20 % EtOAc/*n*-hexane). $[\alpha]^{23}_D$ 0.0 (*c* 6.5

in DCM). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.78 – 3.70 (1H, m), 3.68 (3H, s), 3.50 – 3.41 (1H, m), 2.50 – 2.41 (2H, m), 2.35 – 2.15 (3H, m), 2.10 – 1.85 (3H, m) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 213.6, 170.9, 57.4, 52.9, 46.7-46.9 (d, $J_{C\text{-}F}$ = 16 Hz), 37.9, 34.7, 27.2, 19.6 ppm. ^{19}F-NMR: δ 51.9 (1F, t, $J_{H\text{-}F}$ = 4 Hz) ppm.

Procedure for the synthesis of methyl-1-(2-(fluorosulfonyl)ethyl)-2-oxocyclopentanecarboxylate (23) using hydrogen bonding catalyst 20

A mixture of methyl 2-oxocyclopentane carboxylate (100 mg, 1 equiv.) and *N*-[3,5-Bis(trifluoromethyl)phenyl]-*N*'-[(9*R*)-6'-methoxy-9-cinchonanyl]thiourea (0.1 equiv.) was stirred in toluene (4 mL) at room temperature. To this, ethenesulfonyl fluoride (3 equiv.) was added. The reaction progress was monitored by GC-MS. Upon completion, the reaction mixture was diluted with DCM and passed through a small amount of silica. The solvent was removed under reduced pressure to afford the product as a colourless oil (96 %). R_f = 0.44 (20 % EtOAc/*n*-hexane). $[\alpha]^{23}_{D}$ -33.9 (*c* 8.85 in DCM). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 3.78 – 3.70 (1H, m), 3.68 (3H, s), 3.50 – 3.41 (1H, m), 2.50 – 2.41 (2H, m), 2.35 – 2.15 (3H, m), 2.10 – 1.85 (3H, m) ppm. ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 213.5, 170.9, 57.4, 53.0, 46.9-46.7 (d, $J_{C\text{-}F}$ = 16 Hz), 37.9, 34.8, 27.2, 19.6 ppm. ^{19}F-NMR: δ 52.0 (1F, t, $J_{H\text{-}F}$ = 4 Hz) ppm.

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CHAPTER 5

Description

This chapter contains a crystallographic paper which was a result of a crystal grown from the compounds synthesized in **Chapter 4**. It must be noted that only the title page, results and discussion section of the publication is included. For further supplementary information on this publication, please refer to the CD accompanying this thesis.

Synthesis, characterization and crystal structure of methyl 1-(2-(fluorosulfonyl)-ethyl)-2-oxocyclopentanecarboxylate,C9H13FO5S.

Kimberleigh B. Govender, Marivel Samipillai, Thavendran Govender, Hendrik G. Kruger and Naicker Tricia*

University of KwaZulu Natal, Catalysis and Peptide Research Unit, Durban, 4000, South Africa

Correspondence email: naickert1@ukzn.ac.za

Abstract $C_9H_{13}FO_5S$, triclinic, $P\bar{1}$ (No. 2), a = 5.9390 (3) Å, b = 8.1581 (4) Å, c = 11.3823 (8) Å, β = 98.328 (3)^o, V = 1046.45 (9) Å^3, Z = 2, $R_{gt(F)}$ = 0.0252, $wR_{ref}(F^2)$ = 0.0600, T = 100 K.

1. Experimental

Source of materials:

A mixture of methyl 2-oxocyclopentane carboxylate (20 mg, 1.0 equiv.), thiourea (0.20 equiv.) and DIPEA (0.20 equiv.) was stirred in toluene (1.0 mL) at room temperature. To this, ethenesulfonyl fluoride (3 equiv.) was added. The reaction progress was monitored by GC—MS. Upon completion, the reaction mixture was diluted with DCM and passed through a small amount of silica. The solvent was removed under reduced pressure to afford the product as a colourless oil (80%). R_f = 0.44 (20% EtOAc/n-hexane). ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.78 – 3.70 (1*H*, m), 3.68 (3*H*, s), 3.49 – 3.40 (1*H*, m), 2.50 – 2.42 (2*H*, m), 2.35 – 2.27 (1*H*, m), 2.24 – 2.19 (2*H*, m), 2.11 – 1.84 (3*H*, m) p.p.m. ^{19}F-NMR: 52.0 (1*F*, t, $J_{H—F}$ = 5 Hz) p.p.m. ^{13}C-NMR ($CDCl_3$, 100 MHz): 213.6, 171.0, 57.4, 53.0, 46.8 (d, $J_{C—F}$ = 18 Hz), 38.0, 34.9, 27.2, 19.6 p.p.m. The product was dissolved in n-hexane and subsequent evaporation yielded colourless crystals in 2 days.
Crystal data, data collection and structure refinement details are summarized in Table 1.

2. Results and discussion

Discussion Sulfonyl fluorides (SF) are considered as a versatile functional group owing to its widespread applications [1–5]. The moiety has sparked interest in drug discovery, as it has shown to be an inhibitor for numerous proteins [6,7]. Recently, the SF functional group has been included as a click reagent[8]. Despite this, there are very few references in the literature which highlights the SF group as synthetic intermediates. Currently, our work is aimed at fully investigating the synthetic potential of the SF group[9–10].
Crystal structure analysis of title compound revealed the cyclopentane moiety of the molecule is distorted as one of the carbon atom (C5) is tipped up towards the direction of methylcarboxylate moiety. The 2-(fluorosulfonyl) ethyl and methylcarboxylates substitutions attached are almost in perpendicular to each other. The packing analysis of crystal structure also showed that the molecules in the crystals are interconnected through various C—H···O interactions. Among these, the two important C—H···O interactions that played a vital role in connecting the molecules in the crystals are formed between (i) the fluorosulfonyl group and cyclopentane H-atoms and (ii) fluorosulfonyl and methylcarboxlyate groups. Thus, these interactions help the molecules to form a layered structure made up by chains running along [110] plane. It is also important to note that the F^- atom is not involved in any intermolecular interactions.

3. Synthesis and crystallization

Experimental details: Crystal data, data collection and structure refinement details are summarized in Table 1. A l l non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in idealized positions and refined in riding models with Uĩso~ assigned the values to be 1.2 or 1.5 times those of their parent atoms and the constraint distances of C —H ranging from 0.95 \%A to 1.00 \%A.

Table 1

Experimental details

Crystal data	
Chemical formula	$C_9H_{13}FO_5S$
M_r	252.25
Crystal system, space group	Triclinic, $P\overline{1}$
Temperature (K)	293
a, b, c (Å)	5.9390 (3), 8.1581 (4), 11.3823 (8)
α, β, γ (°)	89.498 (3), 85.314 (5), 84.916 (5)
V (Å^3)	547.48 (5)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.31
Crystal size (mm)	0.32 × 0.27 × 0.17
Data collection	
Diffractometer	Bruker *APEX*-II CCD
Absorption correction	–
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	18679, 2701, 2525
R_{int}	0.015
(sin $\theta/\lambda)_{max}$ (Å^{-1})	0.669
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.030, 0.081, 1.03
No. of reflections	2701
No. of parameters	146
H-atom treatment	H-atom parameters constrained
ρ_{max}, ρ_{min} (e Å^{-3})	0.48, −0.59

Computer programs: *SAINT* (Bruker AXS Inc., Madison, USA, 2006)[11], *SAINT-Plus* and *XPREP* (Bruker, 2008)[12], *SHELXS97* (Sheldrick, 1997)[13], *SHELXS2014* (Sheldrick, 2014)[13], *X-SEED* (Barbour, 2001)[15], *ORTEP-3* [16].

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CHAPTER 6

Summary and Outlook

The application of ESF as a new substrate in homogenous catalysis to afford new sulfonyl fluoride derivatives was successfully achieved. Both transition metal catalysis and organocatalysis were investigated. A novel oxidative Heck reaction was developed where various aryl boronic acids were reacted with ESF to afford a number of substituted *β*-aryl ethenesulfonyl fluorides in good yields (up to 80 %). The developed method was shown to be operationally simple, proceeding under mild reaction conditions and without the addition of ligands, while providing chemoselectivity and *E*-isomer selectivity. The synthetic potential of the method was also investigated and it was found that a simple addition of methylamine to the procedure resulted in the formation of novel *β*-sultams, which can be obtained *via* a one-pot method. Thereafter, the application of this method was investigated and it was applied to the synthesis of a biologically active compound *viz.* Naratriptan. The attachment of the ESF onto the desired indole scaffold was successful. Once converted to the corresponding *β*-sultam, an Aldol condensation was attempted to attach a piperidine onto the indole scaffold. It was found that the basic conditions used resulted in a novel ring opening reaction for the *β*-sultams, producing vinyl sulfonamides. The vinyl sulfonamide requires further reduction before the piperidine can be attached and the desired Naratriptan obtained. Lastly, the ESF was successfully used as a substrate in organocatalyzed Michael reactions. Various organocatalysts, with varying modes of action, were tested and it was found that a thiourea based hydrogen bonding catalyst provided the best reactivity when ESF was reacted with cyclic *β*-ketoesters. The resultant product was obtained in high yields (96 %), but determination of the *ee* proved problematic. The enantioselectivity of the reaction was confirmed by measuring the optical rotation of the product. Confirming the formation of the racemate was also challenging, however a crystal of the racemate was grown. Analysis of the crystal confirmed the formation of the racemate. The use of ESF as a substrate in organocatalysis is novel and this result opens a door for a variety of ESF derivatives *via* this route.