

Regioselective Methylation of α -Trifluoromethanesulfonyl
Carbonyl Compounds and Iridium Catalyzed
Decarboxylative Allylation of
Allyl 3,5-Bis(trifluoromethylphenyl)sulfonylacetate

by

Han Il Kong

A thesis submitted to the Faculty of Graduate and Postdoctoral
Affairs in partial fulfillment of the requirements for the degree of

Master of Science

in

Chemistry

Carleton University
Ottawa, Ontario

© 2011

Han Il Kong



Library and Archives
Canada

Published Heritage
Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et
Archives Canada

Direction du
Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

ISBN: 978-0-494-87854-5

Our file Notre référence

ISBN: 978-0-494-87854-5

NOTICE:

The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:

L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protègent cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

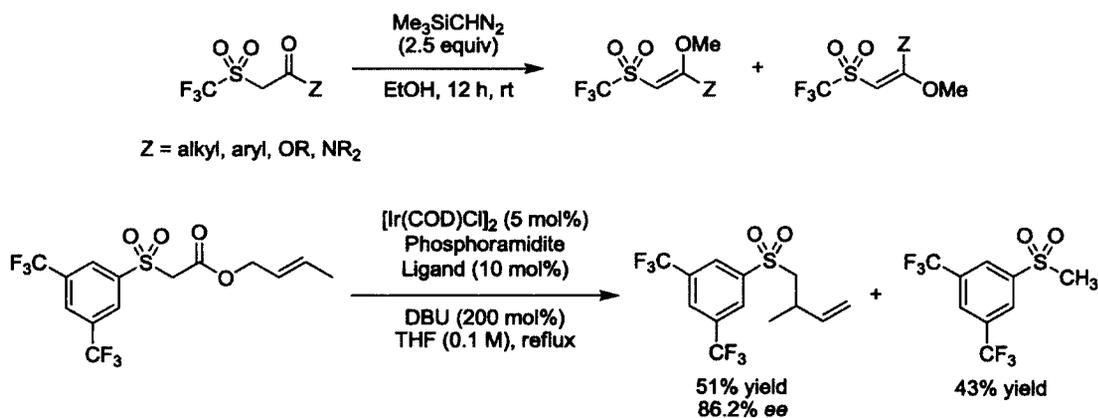
Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

Abstract

The research focus in our group is the development of transition metal catalyzed decarboxylative allylation on electron deficient α -sulfonyl esters in a regio- and enantioselective fashion. Our first sulfonyl substrate was trifluoromethanesulfone (triflone). The alkylation of allyl α -trifluoromethanesulfonyl (triflyl) acetate was more challenging than anticipated, due to the high acidity of our compounds. To take advantage of the acidity, trimethylsilyl diazomethane was examined for the methylation, and the reactivity of different α -triflyl carbonyl systems afforded disparate results. Contrary to the desired C-methylation, the reaction had resulted in mostly O-methylation to afford ambiphilic alkenes.

The other electron deficient sulfone explored in our group was 3,5-bis(trifluoromethyl)phenylsulfone. Crotyl 3,5-bis(trifluoromethylphenyl)sulfonylacetate was treated with iridium^(I) and a chiral phosphoramidite ligand, resulting in the decarboxylative allylation with high regioselectivity and enantioselectivity. The yield was moderate and there was significant amount of byproduct formation; thus, further optimization of the reaction is required.



Acknowledgements

I would like to give special thanks to my supervisor, Dr. Jeffery Manthorpe, for incredible guideline and knowledge, and teaching me a whole new level of the organic chemistry. I consider myself very fortunate to work for him in the laboratory. He has been more supportive and accommodating than anyone. Also I thank lab-mates and my dear friends, Monica Gill and John Palko, for their kind supports and helps in the lab. Monica Gill, who has very kind heart, always has been providing the best help in every corner of our lab without any hesitation. John Palko, my long time lab-mate, has always tried to make the most enjoyable lab-atmosphere. I always appreciated that.

I would also like to thank Dr. Jeffery Smith and his group for technical knowledge and eagerness to assist me in MS. And another thank to Keith Bourque for technical help in NMR.

Above all, none of this would have been possible if it were not for my parents who have always believed in me and encouraged me to pursue my interests. I can't thank them enough for their endless love.

무엇보다 제 가족인 아버지, 어머니, 동생에게 감사합니다.

Publications

Through this research project, two publications are written – an initial communication in *Tetrahedron Letters* and a full paper has been submitted.

Kong, H. I.; Crichton, J. E.; Manthorpe, J. M. Stereoselective Synthesis of Ambiphilic Alkenes via Regioselective Methylation of α -Trifluoromethanesulfonyl Carbonyl Compounds with Trimethylsilyldiazomethane. *Tetrahedron Lett.* **2011**, *52*, 3714-3717.

Kong, H. I.; Gill, M. A.; Hrdina, A. H.; Crichton, J. E.; Manthorpe, J. M. Reactivity of α -Trifluoromethanesulfonyl Esters, Amides and Ketones: Decarboxylative Allylation, Methylation, and Enol Formation. *In preparation.*

It has also been presented in two conferences in 2010: 21st Quebec and Ontario Mini-Symposium on Biological and Organic Chemistry (QOMSBOC) poster presentation and Ottawa-Carleton Chemistry Institute (OCCI) poster presentation.

Table of Contents

Abstract	ii
Acknowledgements	iii
Publications	iv
Table of Contents	v
List of Tables	vii
List of Schemes	viii
List of Appendices	ix
List of Abbreviations	x
1 Chapter: Introduction to Sulfones	1
1.1 Electron Deficient Sulfonyl Group.....	1
2 Chapter: Trifluoromethyl Sulfones	4
2.1 Alkylation of Trifluoromethyl Sulfones	4
2.1.1 Introduction to Trifluoromethyl Sulfones.....	4
2.1.2 Alkylation of α -Triflyl Carbonyl Compounds	10
2.1.3 Ambiphilic Alkenes	14
2.1.4 Methylation Research Goal	15
2.2 Trifluoromethylsulfone Chemistry	15
2.2.1 Experimental Approach	15
2.2.2 Synthesis of α -Trifluoromethanesulfonyl Carbonyl Compounds	16
2.2.3 Reaction with Trimethylsilyldiazomethane	21
2.2.3.1 α -Trifluoromethanesulfonyl Esters	21
2.2.3.2 α -Trifluoromethanesulfonyl Amides.....	23
2.2.3.3 α -Trifluoromethanesulfonyl Ketones.....	27

2.2.4	Ambiphilic Alkenes	31
2.2.5	Conclusion	33
3	Chapter: Experimental Procedure for Trifluoromethane Sulfones.....	35
3.1	General Experimental.....	35
3.2	Synthesis of α -Trifluoromethanesulfone Amides.....	36
3.2.1	Synthesis of α -Bromoamide	36
3.2.2	Synthesis of α -Triflyl Amide	38
3.3	Synthesis of α -Triflyl Ketones	42
3.4	Reaction with Trimethylsilyldiazomethane with α -Trifluoromethanesulfone Carbonyl Compounds	48
4	Chapter: Decarboxylative Allylation	55
4.1	Introduction to Decarboxylative Coupling Reactions	56
4.1.1	Decarboxylative Allylation Reaction.....	58
4.1.2	Iridium Catalyzed Decarboxylative Allylation.....	61
4.1.3	Decarboxylative Research Goal.....	64
4.2	Iridium Catalyzed Decarboxylative Allylation.....	65
4.2.1	Experimental Approach	65
4.2.2	Preparation of Substrates	66
4.2.3	Iridium Catalyzed Decarboxylative Allylation.....	67
4.2.4	Future Work & Conclusion.....	73
5	Chapter: Experimental Procedure for Decarboxylative Allylation	74
5.1	General Experimental.....	74
5.2	Iridium-Catalyzed Decarboxylative Allylation	75
	References	78

List of Tables

Table 1. Comparison of pK _a values (in DMSO)	3
Table 2. Isohypsical Elimination of Triflones by Thermolysis	9
Table 3. Synthesis of α -Triflyl Amides	17
Table 4. The Ratio of Keto/Enol Content of α -Triflyl Ketones in Various Solvents	19
Table 5. Optimization of the Reaction of Trimethylsilyldiazomethane with Amide 3.....	24
Table 6. Reaction of Trimethylsilyldiazomethane with α -Triflyl Amide	25
Table 7. Reaction of Trimethylsilyldiazomethane with α -Triflyl Ketones.....	27
Table 8. Regioselectivity of Methylation using TMS-diazomethane on α -Triflyl Carbonyl Compounds	34
Table 9. Optimization of DcA Reaction with α -Sulfonyl Ester 38 ^a	68

List of Schemes

Scheme 1. Preparation of Sulfones	1
Scheme 2. Formation of Carbanion and Its Use in C-C Bond Formations.....	2
Scheme 3. Elimination of Sulfones.....	2
Scheme 4. Julia Olefinations.....	3
Scheme 5. Reductive Removal of Triflones	8
Scheme 6. Oxidative Removal of Triflones.....	8
Scheme 7. Isohyptic Removal of Triflones	9
Scheme 8. Decarboxylative Allylation	10
Scheme 9. Decomposition of Allylic α -Triflylacetate During Alkylation.....	11
Scheme 10. Potential Reaction Sites of α -Triflyl Carbonyl Compounds for Methylation	13
Scheme 11. Mechanism of Methyl Esterification of Carboxylic Acid by TMS- diazomethane	14
Scheme 12. Preparation of α -Triflyl Ketones	18
Scheme 13. Methylation of Ethyl Trifluoromethanesulfonyl Acetate 2.....	22
Scheme 14. Reaction Rates of Protonation and Methylation with Ketone and Amide	29
Scheme 15. General Regioselectivity of Transition Metal Catalyzed Allylation.....	56
Scheme 16. Standard Cross-Coupling and Decarboxylative Coupling	57
Scheme 17. Regioselectivity of DcA Reaction.....	60
Scheme 18. General DcA Reaction Schemes with C-, N-, and O-nucleophiles.....	62
Scheme 19. Preparation of Allylic α -bis(trifluoromethyl)phenylsulfonyl Acetates	67
Scheme 20. Carroll Rearrangement on Compound 38	70

List of Appendices

Appendices are on separated attachments.

Appendix A. Spectra of Amide Compounds

A.1 α -Bromoamides

A.2 α -Trifluoromethanesulfonyl Amides 3-8

A.3 Ambiphilic Alkenes 22-26, 33, 34

Appendix B. Spectra of Ketone Compounds

B.1 α -Bromoketones 11, 13, 15

B.2 α -Trifluoromethanesulfonyl Ketones 9, 10, 12, 14, 16

B.3 Ambiphilic Alkenes 29, 28, 30, (*E*)-31, (*Z*)-31, 32

Appendix C. Iridium-Catalyzed Decarboxylative Allylation

C.1 1-((2-Phenylbut-2-en-1-yl)sulfonyl)-3,3-bis(trifluoromethyl)benzene 37

C.2 1-((2-Methylbut-3-en-1-yl)sulfonyl)-3,4-bis(trifluoromethyl)benzene 39

C.3 1-(Methylsulfonyl)-3,5-bis(trifluoromethyl)benzene 42

C.4 1-((2-Phenylbut-3-en-1-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene & 1-((6-Phenylhex-3-en-1-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene 43

List of Abbreviations

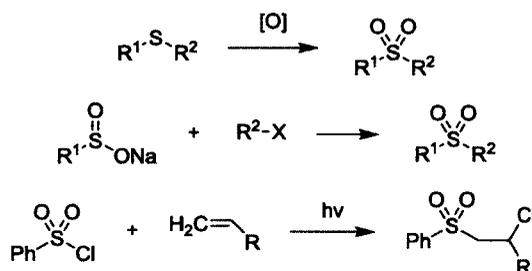
DcA	Decarboxylative allylation
DCM	Dichloromethane
DMA	Dimethylacetamide
DMSO- <i>d</i> ₆	Hexadeuterodimethyl sulfoxide
eq	Equation
equiv	Equivalents
Et	Ethyl
Et ₂ O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
GC	Gas Chromatography
<i>i</i> -PrOH	isopropanol
IR	Infrared
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
NaTf	Sodium trifluoromethanesulfinate
NBS	<i>N</i> -Bromosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser effect spectroscopy
pry	Prydine

<i>p</i> -TSA	<i>p</i> -Toluenesulfonic acid
rt	Room Temperature
S _N 2	Bimolecular nucleophilic substitution
Tf	Trifluoromethanesulfonyl or Trifluoromethanesulfinate
Tf ₂ O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TMS	Trimethylsilyl

1 Chapter: Introduction to Sulfones

1.1 Electron Deficient Sulfonyl Group

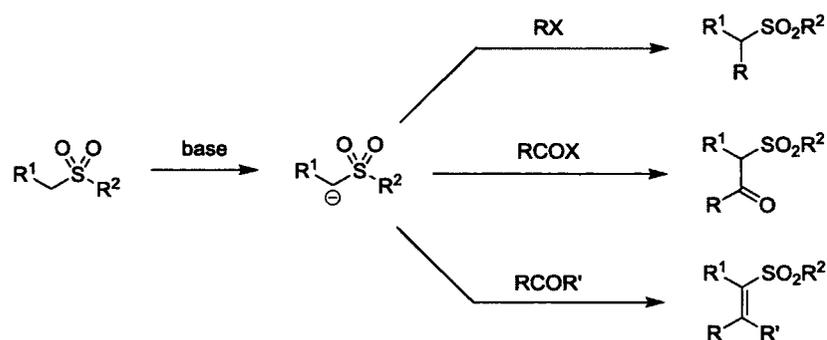
Sulfur has exceptional reactivity and functionality both as an electrophile and as a nucleophile. It forms a number of functional groups with different oxidation states feasible by the contribution of the empty 3d orbitals.¹ Among the most common functional groups, the significance of the sulfone has been growing and the use of it in organic synthesis has been developed over time. Similar to oxygenated carbon, sulfones have been employed not only in many great synthetic methodologies but also in vast array of total syntheses of natural products.² The importance and usefulness of sulfones is derived from the several key aspects of properties and reactivity.³



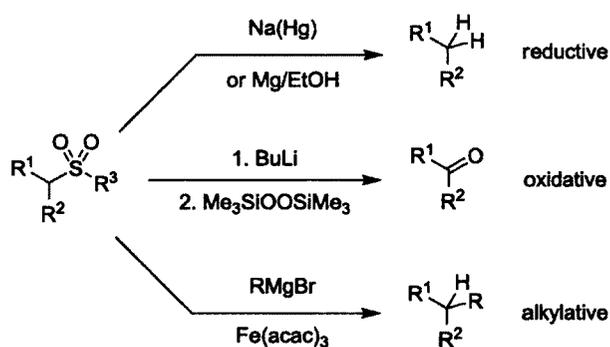
Scheme 1. Preparation of Sulfones

Sulfones are easily prepared by a wide range of methods, including, among others, simple sulfides oxidation, alkylation of sulfinate salts, and free-radical addition of sulfonyl halides (Scheme 1). Sulfones also allow for the formation of carbanions in the position α to the sulfone due to its strong electron withdrawing character. These carbanions can then be subjected to various C-C bond formations like Claisen,⁴ Michael,⁵ or Knoevenagel reactions,⁶ or they can be halogenated or nitrated (Scheme 2). Finally,

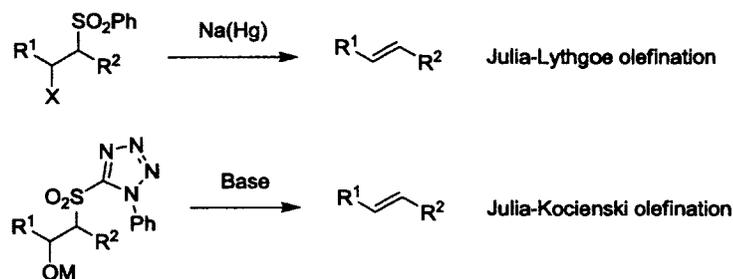
the most important strategic aspect, the sulfone group can be easily removed from the molecule once it serves its function in synthesis as an activating group for C-C and C=C bond formation. A sulfone, unlike the carbonyl group or other oxygenated functionalities, is often not desired in the targeted molecules. One of the most common methods of the elimination is a reductive cleavage; other eliminations include the oxidative and alkylative desulfonylation (Scheme 3).⁷ Another use of the elimination of sulfone is the formation of C=C bond, known as the Julia olefination (Scheme 4).⁸



Scheme 2. Formation of Carbanion and Its Use in C-C Bond Formations



Scheme 3. Elimination of Sulfones



Scheme 4. Julia Olefinations

A sulfonyl group, depending on the substituents on the sulfur, can impart unique and diverse properties to molecules. For example, the pK_a of a hydrogen adjacent to a sulfone is acidic. The pK_a value can be varied by the inductive effect from different substituents (Table 1). The trifluoromethanesulfonyl (CF_3SO_2-) moiety imparts the highest acidity as one of the strongest neutral electron-withdrawing group. As result of its strong inductive effect, the triflyl group has a distinct reactivity, which can be used in various ways to develop new synthetic tools. Thus, our research group is developing new methodologies using the electron deficient trifluoromethylsulfone (triflone).

Table 1. Comparison of pK_a values (in DMSO)

R ₁	R ₂	pK _a
CH ₃	H	31.1 ⁹
Ph	H	29.0 ¹⁰
CF ₃	H	18.8 ¹¹
CF ₃	Ph	14.6 ⁴
CF ₃	CO ₂ Et	6.40 ¹²
CF ₃	SO ₂ CF ₃	2.1 ⁴

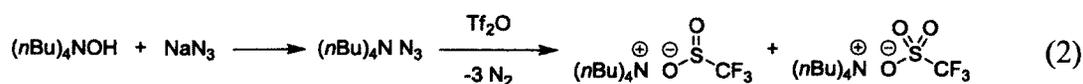
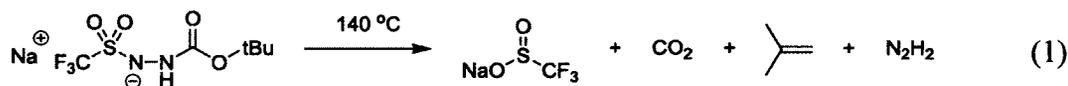
2 Chapter: Trifluoromethyl Sulfones

2.1 Alkylation of Trifluoromethyl Sulfones

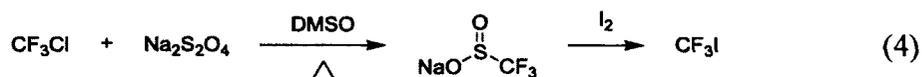
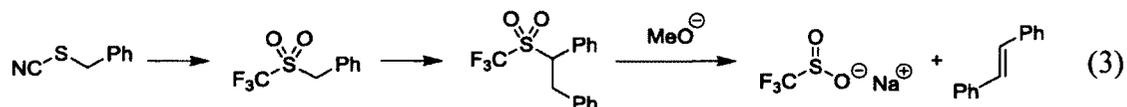
2.1.1 Introduction to Trifluoromethyl Sulfones

The replacement of alkyl or aryl moieties in typical sulfones with more electronegative moieties makes the sulfonyl group more electron deficient. With a stronger electron-withdrawing substrate, the sulfone can more easily stabilize an adjacent negative charge, which may facilitate subsequent C-C bond formation reactions. For this reason, the trifluoromethanesulfonyl group (triflyl, CF_3SO_2^-) is drawing particular attention. The triflyl group is known as one of the strongest neutral electron-withdrawing groups.

James B. Hendrickson is a pioneer in triflone chemistry and has developed methods to prepare, use, and eliminate triflone group. The triflyl groups may be introduced either as an electrophile or nucleophile. The primary electrophilic source of the triflyl group is the very reactive triflic anhydride (Tf_2O). The main nucleophilic source of triflyl is triflate anion. Potassium triflate can be prepared,¹³ but this salt was quite hygroscopic and is used immediately after the preparation. Alternatively, the non-hygroscopic sodium triflate has been prepared by a pyrolysis of the sodium salt of *N*-triflyl-*t*-butyl carbazate (eq 1).¹⁴ Another simple preparation of triflate salt was the decomposition of triflyl azide using a quaternary ammonium counterion (eq 2).¹⁵

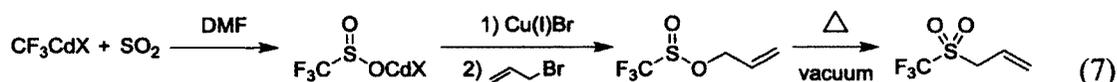
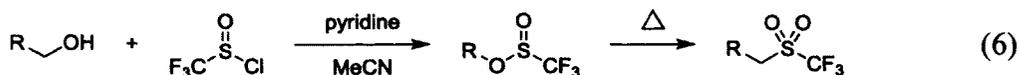
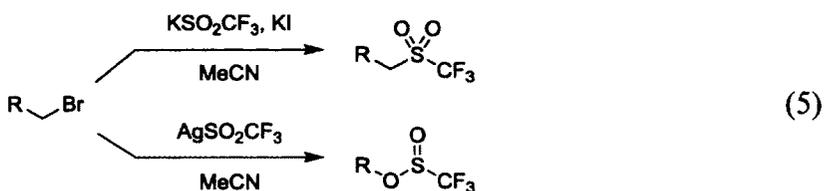


There are also other methods of preparation for sodium triflate.¹⁶ Yezeguleian has proposed a preparation of triflate salts by β -elimination of aliphatic triflones bearing an acidic hydrogen in β position (eq 3). Chen has presented sodium triflate as an intermediate toward the perfluoroalkyl iodides from perfluoroalkyl chlorides (eq 4).



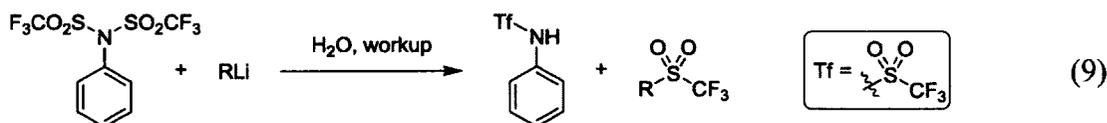
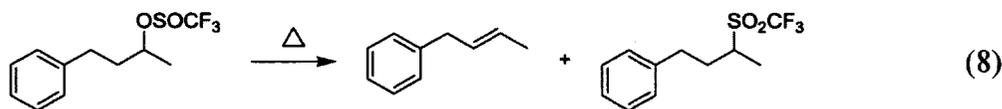
In general, both electrophilic and nucleophilic triflyl compounds are stable and feasible to prepare. As it is a sulfone group, the practical interests of triflyl group in the organic synthesis involve the initial attachment to molecules, subsequent refunctionalization reactions, and finally the removal of the triflyl group.

Triflones have been of particular interest to activate the C-C bond formation. A common approach to the preparation of triflones is the $\text{S}_{\text{N}}2$ reaction of the nucleophilic triflate anion on alkyl halides. In this case, triflate anions could proceed with either S- or O-alkylation.^{13,17} Potassium triflate favored the S-alkylation while silver triflate favored O-alkylation resulting in the formation of the corresponding triflate ester (ROSO_2CF_3) (eq 5), which may also be prepared from an alcohol and triflyl chloride. Triflate esters are converted to the thermodynamically more stable triflone in a polar solvent such as HMPA and high temperature (145-155 °C) (eq 6). Burton has used this rearrangement to form allylic triflones from trifluoromethylcadmium, which was prepared by an insertion of perfluorocadmium reagent into SO_2 (eq 7).¹⁸



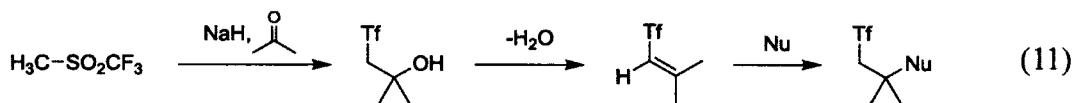
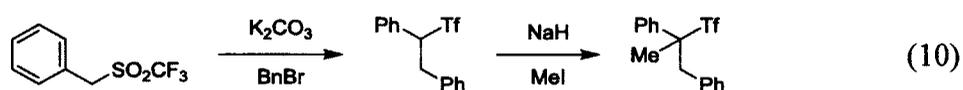
X = halide

Unfortunately these methods of triflone formation were limited to primary halides, because the nucleophilicity of triflate anion was not strong enough to replace non-primary halides. It was preceded to make secondary triflate esters from secondary alcohol and triflinyl chloride and it was attempted to rearrange to the secondary triflone; however, when they were subjected to the high temperature, they underwent the elimination of the triflyl group to form alkenes, instead of the thermal rearrangement to the secondary triflone (eq 8).¹³ Another method for the preparation of the triflone was the use of a primary or secondary alkyllithium reagent with an electrophilic triflyl source, *N*-phenyltriflimide, and Hendrickson have produced 2-triflylbutane using *sec*-butyllithium (eq 9).¹⁹



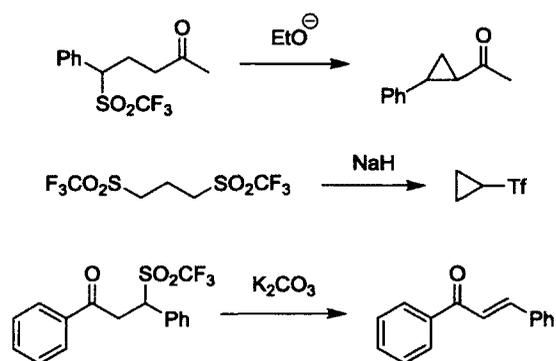
Although these preparation methods mainly apply to primary triflones, it was not a synthetic limitation for the triflyl group. Triflones allow a very facile formation of α -

carbanion with a mild base due to the strong electron-withdrawing effect, and the subsequent alkylation was readily carried out with an alkyl halide to build secondary, and tertiary triflones (eq 10).^{13,14,17} Also the triflyl carbanion reacted with carbonyl groups similar to the Claisen or aldol condensation.²⁰ β -Hydroxyltriflone from the aldol reaction was readily dehydrated to the α,β -unsaturated triflone, which allowed the 1,4-conjugated addition (eq 11). Moreover, the α,β -unsaturated triflone was an active dienophile in the Diels-Alder reaction.¹³



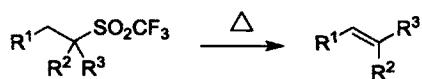
The removal of triflyl group had been developed in three ways: reductive, oxidative, and isohypsic removals. In the reductive removal (Scheme 5),^{13,17} the treatment of triflones with Raney nickel resulted in the hydrogenolysis of triflyl groups, whereas the platinum-catalyzed hydrogenation of olefinic triflones led to the reduction of the alkene without the cleavage of triflones as long as it was not benzylic. For α -triflyl carbonyl compounds, under mild conditions, zinc in ethanol reductively cleaved triflyl groups quantitatively. Also the reduction of triflones to the thiol was achieved by LiAlH_4 , while NaBH_4 or aluminum amalgams were ineffective.

thermal elimination, the primary triflone was very stable, but when the α -carbon was substituted, the elimination became more feasible (Table 2).



Scheme 7. Isohyspic Removal of Triflones

Table 2. Isohysical Elimination of Triflones by Thermolysis



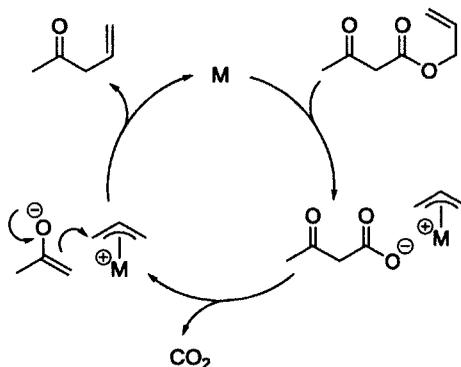
R ₁	R ₂	R ₃	Temp (°C)
Ph	H	H	Stable < 300
Ph	H	Ph	200
PhCO	H	Ph	160
Ph	PhCH ₂	CH ₃	180
Ph	CH ₃	Ph	70

The series of reactions introduced in this section demonstrate the utility of the triflone group in the synthesis. The ability to introduce the triflone group in an electrophilic or nucleophilic fashion provided the flexibility for the design of further reactions as it was easily attached and yet easily removed in various ways. For us, the

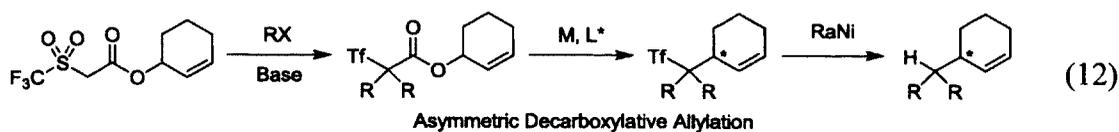
stable carbanion formation drew a particular interest in the development of new reactions activated by the triflyl groups.

2.1.2 Alkylation of α -Triflyl Carbonyl Compounds

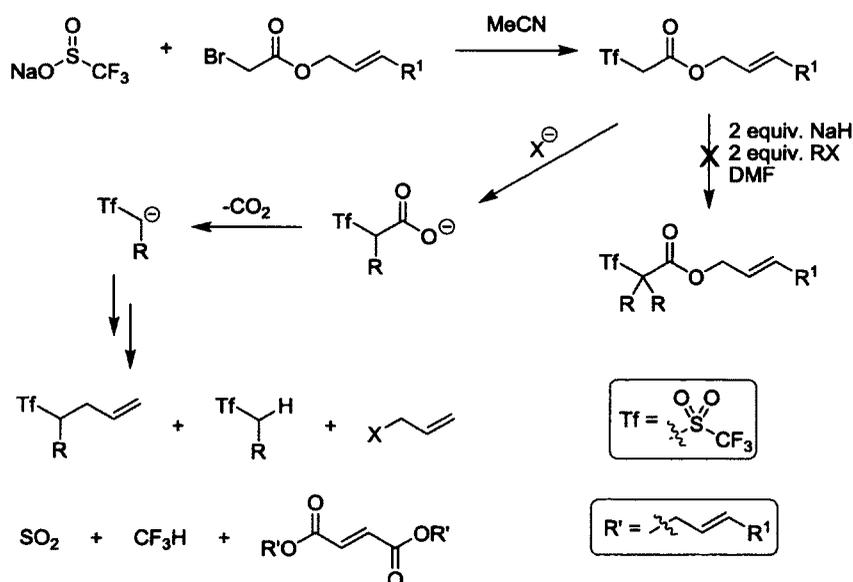
We had envisioned taking advantage of the stability of α -carbanion of trifluoromethyl sulfone to facilitate the decarboxylative allylation (DcA) reaction, which is introduced with more details in section 4.1.1. In general, the β -keto allyl ester substrate undergoes transition metal-mediated decarboxylation to generate a stable enolate and a metal-allyl complex, followed by the reductive elimination to give γ,δ -unsaturated ketone (Scheme 8). The formation of the stable enolate intermediate is the driving force for the decarboxylation. As introduced in the previous section, triflone groups are known to stabilize α -carbanions, so that such a substrate of α -triflyl allyl ester is anticipated to undergo the decarboxylative allylation. Furthermore, two strong electron-withdrawing groups of sulfone and ester would allow form alkylation at the α -carbon to form a quaternary carbon before the DcA reaction. The triflone could be cleaved or re-functionalized into other groups as discussed in previous section (eq 12).



Scheme 8. Decarboxylative Allylation

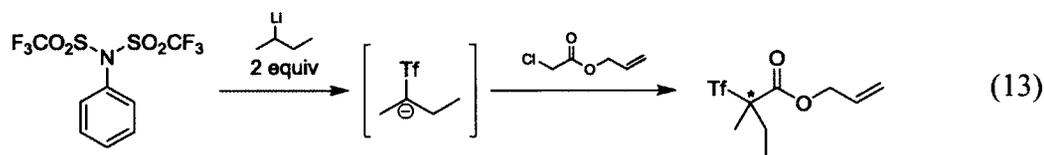


The preparation of appropriate substrates had been simply planned with nucleophilic S_N2 reaction of sodium trifluoromethanesulfonate (NaTf) and allylic haloacetate, followed by the alkylation at the α -carbon. After the formation of allyl α -triflylacetate, the attempted alkylation at the α -carbon using typical conditions of the exposure to base and alkyl halide was unsuccessful. Moreover, when the reaction was forced with excess amount of alkyl halide and high temperature, it resulted in the decomposition of α -triflyl ester by the nucleophilic attack of the halide, leading toward multiple byproducts. Langlois and Laurent had studied intensively on the preparation of ethyl α -triflylacetate using NaTf and identified a number of byproducts, which could be caused by the nucleophilic attack of halides (Scheme 9).²² The difficulty of alkylation at α -carbon was thought to be due to the high acidity of α -triflyl ester compound (pK_a 6.40 in DMSO),¹² resulting in its conjugate base being too stable for alkylation to take place.

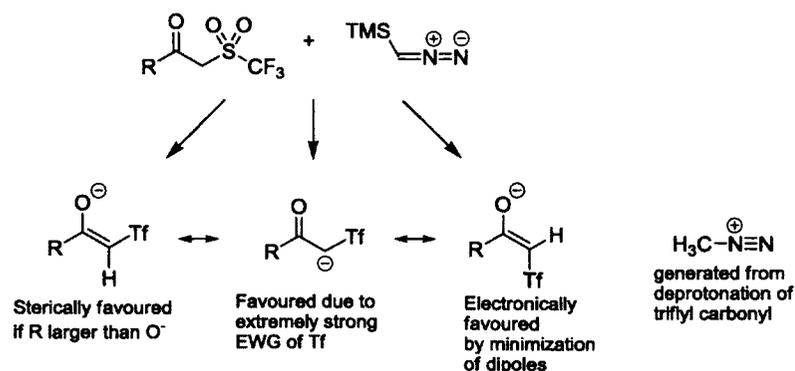


Scheme 9. Decomposition of Allylic α -Triflylacetate During Alkylation

Another synthetic route to such dialkylated substrates was proposed using the electrophilic triflyl source, *N*-phenyltriflimide.¹⁹ The reaction with organolithium compounds, such as *n*-BuLi and *sec*-BuLi, generated alkyltriflones, and the excess amount of organolithium compounds led to the formation of the α -carbanion which could be quenched with various electrophiles to give the tertiary and quaternary triflones. In our group, this method had successfully yielded allyl 2-methyl-2-(trifluoromethylsulfonyl)butanoate (eq 13).²³ However, this synthetic pathway was not readily varied since it required the secondary alkylolithiums and only a few are commercially available. Moreover, the preparation of alkylolithiums was considerably more tedious than the corresponding Grignard reagents.



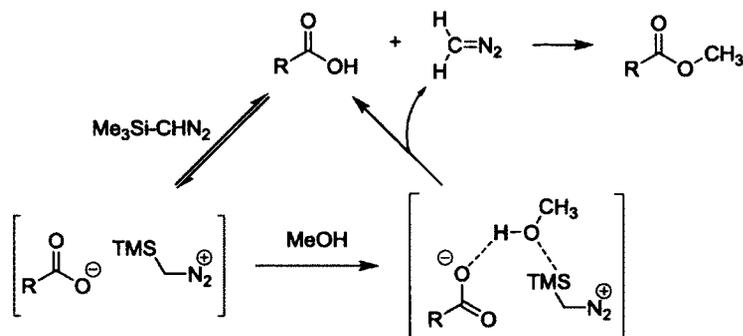
As previously discussed, the pK_a of α -triflyl esters is approximately 6.40. The similarity of this pK_a value with acetic acid (pK_a 12.6 in DMSO) caused us to investigate the possibility of alkylating with diazoalkanes, which are well known to alkylate carboxylic acids. Given the triflone group's strong electron withdrawing character and ability to stabilize negative charge, it results in high electron density on the α -carbon of the triflone carbanion rather than the enolate resonances,¹² so that the C-enolate would be alkylated to give the α -substituted α -triflyl ester. However, since diazoalkanes are "hard" reagents, it was unclear if the alkylation would occur at the oxygen of enolates or the α -carbon of triflone carbanion (Scheme 10).



Scheme 10. Potential Reaction Sites of α -Triflyl Carbonyl Compounds for Methylation

Diazomethane, unfortunately, is toxic, flammable, photosensitive, thermally unstable, and shock sensitive. On the other hand, the trimethylsilyl (TMS) derivative of diazomethane is a stable gas that can be easily handled as a commercially available solution in ether or hexanes. Moreover it exhibited the same reactivity when the reaction was conducted in methanol. Its mechanistic activity had been established as the methylation proceeded via the methanolytic protodesilylation (Scheme 11).²⁴ The carboxylic acid acts as a catalyst; first as a general acid to protonate the TMS-diazomethane, and then as a general base for the methanolysis to generate free diazomethane, which quickly reacted with the carboxylic acid.

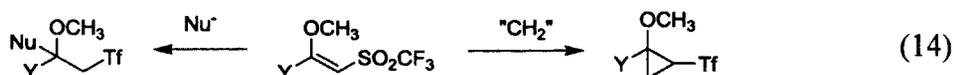
Due to the safety and ease of handling, the TMS diazomethane was used to investigate the methylation reactivity of α -triflyl carbonyl compounds.



Scheme 11. Mechanism of Methyl Esterification of Carboxylic Acid by TMS-diazomethane

2.1.3 Ambiphilic Alkenes

Although C-alkylation was the desired outcome, the treatment of α -triflyl carbonyl compounds with TMS-diazomethane had the potential to result in the O-methylation. Even if the O-methylation was preferred, it would result in the formation of vinyl triflones. In comparison to alkyl and aryl triflones, allyl and vinyl triflones have not been studied in depth. The interesting aspect of vinyl triflones derived from α -triflyl carbonyl compounds is that they would be ambiphilic alkenes. These alkenes would have both strong electron-withdrawing group and electron-donating group; in this case, a triflyl and methoxy group on each end of double bond would make the compound both an electrophile and a nucleophile. Such compounds might further increase the value of the triflone in synthesis, as they could be electrophiles for the nucleophilic addition or be substrates for cycloadditions, including cyclopropanation to afford a new class of donor-acceptor cyclopropanes (eq 14).²⁵



(14)

2.1.4 Methylation Research Goal

The preparation of the desired α -alkylated α -triflyl carbonyl compounds is not achieved by typical alkylation conditions (Scheme 9). Diazomethane has provide a new direction to methylate α -triflylcarbonyl compounds; however, there are two potential reaction sites for the methylation; the α -carbon which has the high electron density due to the strong electron withdrawing effect of the triflone group, and the carbonyl oxygen which is the “hard” site of the enolate form (Scheme 10). It is unclear whether the methylation would take place at the α -carbon of triflone carbanion or the oxygen of enolate. Thus, this is explored with TMS-diazomethane on various α -triflyl carbonyl compounds.

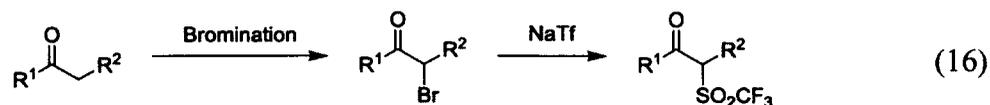
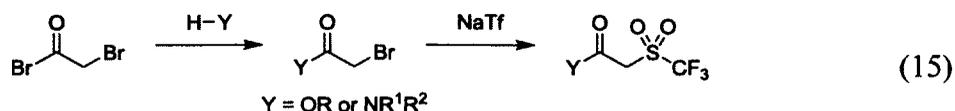
2.2 Trifluoromethylsulfone Chemistry

2.2.1 Experimental Approach

The preliminary step towards the alkylation of α -trifluoromethansulfonyl carbonyl compounds with TMS-diazomethane was the preparation of adequate substrates. This was easily achieved from inexpensive, commercially available compounds such as bromoacetyl bromide. A wide range of α -bromoesters and α -bromoamides were prepared by nucleophilic substitution with requisite alcohols and amines. For α -bromoketones, some were commercially available; others were prepared via α -bromination.

These α -bromo carbonyl compounds were then subjected to S_N2 reaction with sodium trifluoromethanesulfinate (NaOSOCF₃, NaTf) to give α -triflyl carbonyl compounds. Once α -triflyl carbonyl substrates were in hand, they were tested for

reactivity with TMS-diazomethane and the selectivity of the methylation site between the oxygen and the α -carbon.

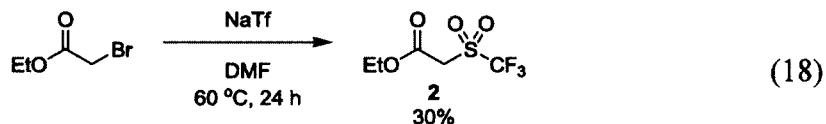
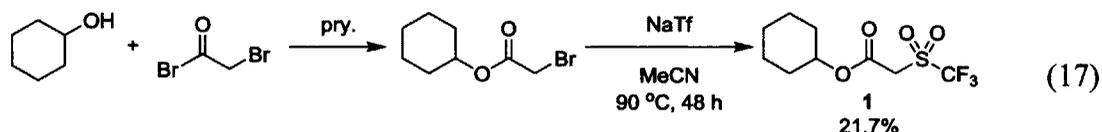


2.2.2 Synthesis of α -Trifluoromethanesulfonyl Carbonyl Compounds

The preparation of α -trifluoromethanesulfonyl (triflyl) carbonyl compounds was done primarily using α -bromocarbonyl compounds, which were commercially available or made from bromoacetyl bromide.

For α -triflyl esters, cyclohexyl α -triflylacetate was prepared from bromoacetyl bromide and cyclohexanol, followed by a S_N2 reaction with NaTf in MeCN (eq 17).

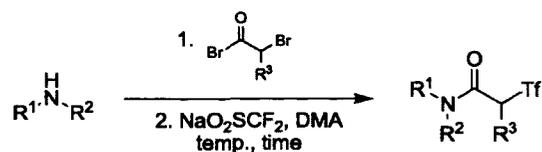
Ethyl α -triflylacetate was easily made in the same manner from commercially available ethyl bromoacetate (eq 18).^{22,26}



A selection of α -triflyl amides was prepared from 2 equivalents of the corresponding amines and bromoacetyl bromide or 2-bromopropinyl bromide, followed by S_N2 reaction with sodium trifluoromethanesulfinate in DMA (Table 3). As the alkyl moieties on the amide were small, the S_N2 reaction with NaTf occurred relatively easily

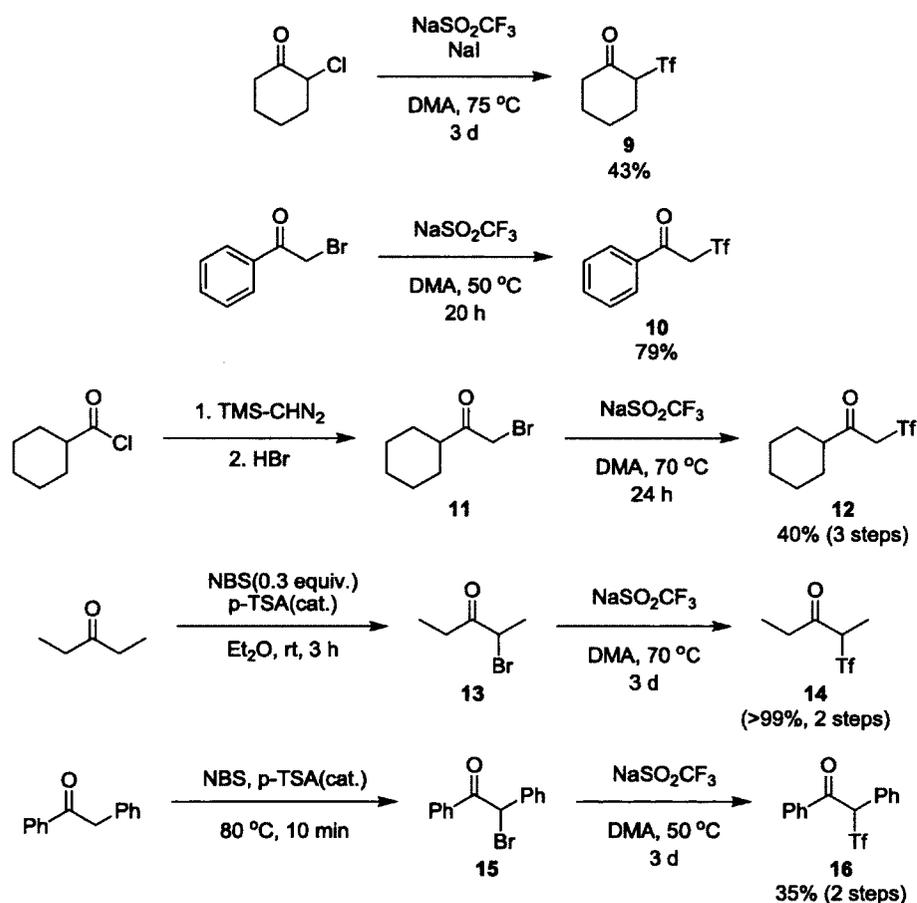
(entries 1 and 3). The presence of substitution at the α -carbon increased the steric hindrance for a nucleophilic attack, thus it resulted in the low yield even with long reaction time and excess amount of NaTf (entry 6).

Table 3. Synthesis of α -Triflyl Amides



Entry	R ₁ , R ₂	R ₃	NaO ₂ SCF ₃ (equiv)	Step 2 temp, time	Product	Yield (%, 2 steps)
1	(CH ₂) ₄	H	1.5	60 °C, 2 d	 3	90
2	(C ₂ H ₄) ₂ O	H	2.0	70 °C, 3 d	 4	52
3	<i>i</i> -Pr ₂	H	1.5	70 °C, 3 d	 5	54
4	Et ₂	H	1.5	70 °C, 3 d	 6	86
5	Bu, H	H	1.2+0.5 after 2 d	70 °C, 4 d	 7	72
6	(CH ₂) ₄	CH ₃	1.5+0.85 after 4 d	70 °C, 7d	 8	41

A selection of α -triflyl ketones was prepared from requisite α -haloketones (Scheme 12). Those that were not commercially available were prepared by the bromination at the α -carbon from the corresponding ketones using NBS and a catalytic amount of *p*-TsOH. For example, cyclohexanecarbonyl chloride was converted into 2-bromo-1-cyclohexylethanone **11** by a reaction with TMS-diazomethane, followed by the treatment with HBr.²⁷

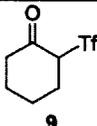
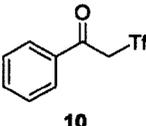
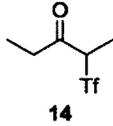
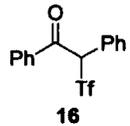
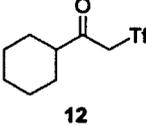


Scheme 12. Preparation of α -Triflyl Ketones

In the case of 2-bromopentan-3-one **13**, the bromination was attempted with pentan-3-one by a solvent-free method reported by Stavber.²⁸ However, this resulted in a

mixture of mono- and di-brominated products, 2-bromopentan-3-one and 2,4-dibromopentan-3-one. The separation of these two compounds was not simple as both are volatile. This problem was overcome by using a limited amount of NBS, and this resulted in the near quantitative yield of 2-triflylpentan-3-one **14** with respect to NBS.

Table 4. The Ratio of Keto/Enol Content of α -Triflyl Ketones in Various Solvents

	Keto/Enol Ratio		
	CDCl ₃	DMSO- <i>d</i> ₆	Acetone- <i>d</i> ₆
 <p>9</p>	1 : 0.53	1 : 6.6	1 : 0.1
 <p>10</p>	1 : 0.06	1 : 0	1 : 0.53
 <p>14</p>	1 : 0	1 : 0.18	1 : 10.9
 <p>16</p>	1 : 0.06	Broad Peaks ^a	1 : 0.25
 <p>12</p>	1 : 0.1	Broad Peaks ^a	1 : 0.36

^a keto/enol tautomerization is occurring at the NMR timescale.

Unlike the α -triflyl amides, some of the α -triflyl ketones exhibited significant enol content, a phenomenon previously observed anecdotally in α -perfluorosulfonyl ketones.²⁹ This was mostly due to the strong electron-withdrawing aspect of the triflyl

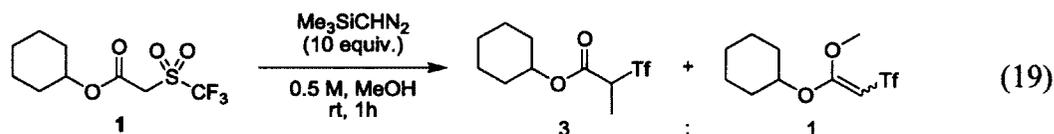
group. The α -triflyl ketones were acidic enough to cause the keto/enol tautomerization. In order to study this phenomenon in depth, the keto-enol ratios of ketones were collected from the ^1H NMR spectra at 1 mM in different deuterated polar solvents, CDCl_3 , $\text{DMSO-}d_6$, and $\text{acetone-}d_6$. As other typical keto/enol tautomerism, it was observed the enol content was higher in more polar solvent (Table 4). 2-Triflyl pentan-3-one **14** exhibited the most typical keto/enol tautomerization with respect to the increasing polarity of the solvent. There was no enol isomer of **14** observed in CDCl_3 . The enol was slightly evident in $\text{DMSO-}d_6$, which is more polar than CDCl_3 . In $\text{acetone-}d_6$, the enol was the major isomer with a ratio of 10.9:1. 2-Triflyl cyclohexanone **9** was a mixture of keto and enol in CDCl_3 , but the enol isomer became highly favored in $\text{DMSO-}d_6$. Unexpectedly, it showed the least amount of enol content in $\text{acetone-}d_6$, which is the most polar solvent. 1-Phenyl-2-triflyl ethanone **10** had a very small amount of the enol isomer in CDCl_3 , and the enol content was increased in $\text{acetone-}d_6$ as expected. However, no enol content was observed in $\text{DMSO-}d_6$. Both 1-cyclohexyl 2-triflylethanone **12** and 1,2-diphenyl-2-triflylethanone **16** had a small amount of the enol isomer in CDCl_3 , and increased enol content in $\text{acetone-}d_6$ as well. However, in $\text{DMSO-}d_6$, the keto/enol ratio could not be determined clearly because the keto/enol tautomerization appeared to be occurring on the NMR timescale, resulting in broad peaks in the ^1H NMR spectra.

A number of α -triflyl carbonyl compounds were successfully prepared from the corresponding halides and using NaTf. With this array of substrates in hand, the reactivity of TMS-diazomethane was tested and the reactive site between the α -carbon and the enolate oxygen was determined.

2.2.3 Reaction with Trimethylsilyldiazomethane

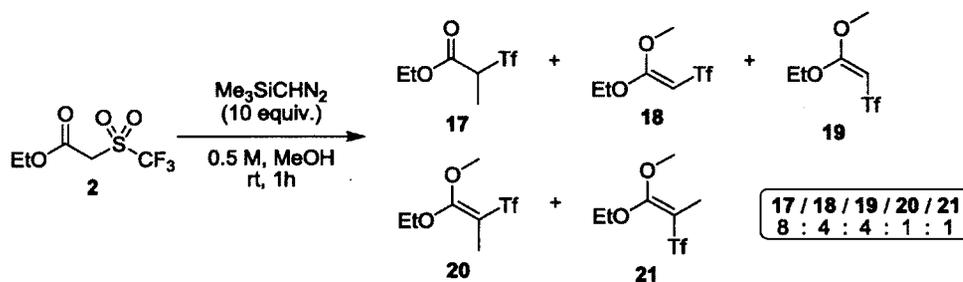
2.2.3.1 α -Trifluoromethanesulfonyl Esters

An initial study of methylation α -triflyl carbonyl compounds with TMS-diazomethane was previously carried out in our research group by an undergraduate student, Jennifer Crichton. An attempt to methylate cyclohexyl 2-triflylacetate **1** was initially performed with 10 equivalents of TMS-diazomethane in MeOH at the ambient temperature (eq 19). The reaction mixture was simply concentrated under vacuum after 1 hour and resulted in a complex mixture of both C- and O-methylation.



The ^1H NMR spectrum of crude product of this reaction resembled both C- and O-methylated products. For the O-methylation, there were two closely spaced singlets at 3.89 and 3.91 ppm, which were considered as methoxy groups, and another two singlets at 4.48 and 4.50 ppm, which were the methine hydrogen ($=\text{CH}$). These two sets of peaks were suspected to be the cis- and trans-isomer from the O-methylated products. It was not determined which one was the major isomer, but the ratio was found as 2:1. For the C-methylation, there was a quartet at 4.25 ppm resembling the hydrogen at α -position, and there was a clear doublet for methyl hydrogen (CH_3) at 1.76 ppm. The crude product was not purified and the methyl hydrogen peak from C-methylated product was overlapping with a multiplet from the cyclohexyl group. Thus the exact ratio of C- and O-methylation could not be determined. It was, however, estimated to be 3:1 ratio for C- to O-methylation based on the ^1H NMR spectrum.

In order to more precisely determine the selectivity ratio of TMS-diazomethane between O and C, the methylation with ethyl 2-triflylacetate **2** was evaluated under the same conditions. In ^1H NMR spectrum, there were two sets of two singlets for methoxy and methylene hydrogen from mono O-methylated product; a complex multiplet at ~ 4.3 ppm resembled the hydrogen at α -position from C-methylated products, along with newly attached methyl group on the α -carbon at 1.78 ppm. Beside these peaks, there were few unexpected peaks close to the methyl group from C-methylation. Some of these multiplets held extra number of hydrogen integration. Considering that 10 equivalents of TMS-diazomethane were used, it was not improbable to anticipate bis-C,O-methylation. Thus, the reaction afforded a 8 : 4 : 4 : 1 : 1 of products from C-methylation (**17**), non-selective O-methylation (**18** and **19**), and non-selective bis-C,O-methylation (**20** and **21**) (Scheme 13).



Scheme 13. Methylation of Ethyl Trifluoromethanesulfonyl Acetate **2**

Although the product distribution was not ideal, it provided the evidence that the necessary reactivity existed. It was surmised that if the selectivity could be tuned in either direction, the products would be useful. Given that the amount of charge borne by the enolate oxygen is determined by the nature of the substituent adjacent to the carbonyl, it

was postulated that carbonyl compounds other than the esters might exhibit the more distinct selectivity in the reaction with TMS-diazomethane.

2.2.3.2 α -Trifluoromethanesulfonyl Amides

From the array of α -triflyl amides that had been synthesized, amide **3** was selected for the optimization of TMS-diazomethane methylation. Treatment with 10 equivalents of TMS-diazomethane at 0.5 M in MeOH for 3 hours resulted in 100% conversion to O-methylated Z-alkene **22** as the single product. There were no C-methylation or di-methylation products observed.

Prior to exploring the methylation of other α -triflyl amide substrates, the reaction conditions were optimized not only to avoid the overuse of TMS-diazomethane but also to prevent possible bis-methylation (Table 5). In order to ensure complete desilylation, the solvent was limited to simple alcohols. Though MeOH is commonly used with TMS-diazomethane, it was found that EtOH was superior for the formation of alkene **22** (entries 7-8). The number of equivalents of TMS-diazomethane was reduced from 10 to 2.5 and the high conversion was maintained (entries 8-9). Further experiments showed that other polar solvents, such as THF, Et₂O, and EtOAc were effective in combination with EtOH in a 1:1 ratio (entries 11-13). Notably, changing the reaction concentration from 0.5 M to 1.0 M did not affect the conversion for alkene **22**, but it was required to achieve full conversion of ketone **11** to alkene **28** (eq 20).

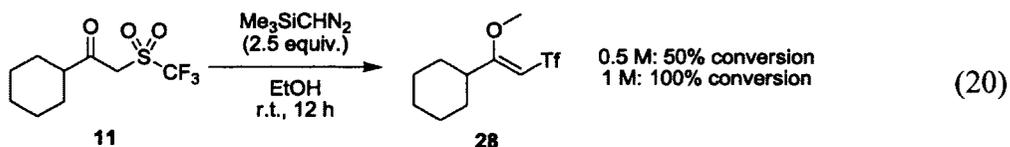
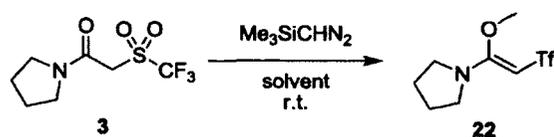


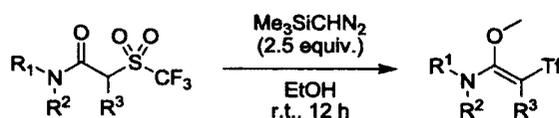
Table 5. Optimization of the Reaction of Trimethylsilyldiazomethane with Amide **3**

Entry	Me ₃ SiCHN ₂ (equiv)	Solvent	Conc. (M)	Time (h)	Conv. (%) ^a
1	10	MeOH	0.5	3	100
2	10	EtOH	0.5	3	100
3	10	<i>i</i> -PrOH	0.5	3	68
4	5	MeOH	0.5	24	100
5	5	EtOH	0.5	24	100
6	5	<i>i</i> -PrOH	0.5	24	86
7	2.5	MeOH	0.5	12	50
8	2.5	EtOH	0.5	12	100
9	2.5	EtOH	1	12	100
10	1.5	EtOH	1	12	47
11	2.5	EtOH/THF ^b	1	12	90
12	2.5	EtOH/Et ₂ O ^b	1	12	94
13	2.5	EtOH/EtOAc ^b	1	12	91

^a Determined by integration of the ¹H NMR spectrum of the crude reaction mixture

^b Mixture of 1:1 ratio in volume

With the optimized reaction conditions using TMS-diazomethane (2.5 equiv.) in EtOH (1.0 M), other α -triflyl amide substrates were subjected to the methylation (Table 6). Amide **4** displayed 100% conversion under the optimized condition as it had similar steric hindrance to amide **3** (entry 2). Amide **5** and **6** exhibited much lower conversion in the 12 hour reaction time, since the aliphatic substituents on nitrogen, diethyl and di-isopropyl, were more hindered than pyrrolindyl (entries 3-4).

Table 6. Reaction of Trimethylsilyldiazomethane with α -Triflyl Amide

Entry	S.M.	Product	Conv. (%) ^a	Yield (%)	Z/E ratio ^b
1			100	74	100:0
2			100	80	100:0
3			29 (12 h) 63 (48 h)	22	100:0
4			65 (12 h) 100 (18 h)	44 (86) ^c	100:0
5			25 (12 h) 45 (60 h)	16 (12 h) 23 (60 h)	100:0
6			0 ^d 0 ^e	-	-

^a Determined by integration of the ¹H NMR spectrum of the crude reaction mixture.

^b Assigned via 2D NOESY experiment.

^c Crude yield.

^d Under Standard conditions.

^e 5 equiv. Me₃SiCHN₂, 1 M in EtOH, rt, 5 d.

Notably, the methyl substituent on the α -carbon of amide **8** completely inhibited the methylation (entry 6). As expected, the Z-alkene was observed exclusively for all amide substrates due to the A^{1,3}-strain interaction in the enolate form (Figure 1).³⁰

Interestingly, a secondary amide, which lacks the $A^{1,3}$ -strain comparing other amide substrates, also afforded the *Z*-alkene exclusively (Table 6, entry 5).

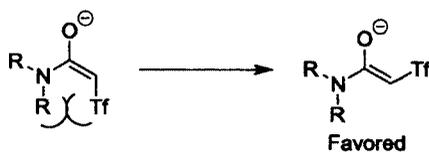


Figure 1. $A^{1,3}$ -strain of Amide Enolate

Unlike any other amide substrate, amide **8** was completely unreactive towards the methylation. For the deprotonation of amide **8**, it is required to adapt the conformation as drawn in Figure 2 (I and II), so that C-H orbital is overlapped with carbonyl π^* orbital. However, the methyl and triflyl substituents at the α -carbon would exhibit high $A^{1,3}$ -interaction with the carbonyl oxygen and the pyrrolidinyl group; thus the most stable and lowest energy level conformation would be as drawn Figure 2 (III), where the C-H bond is anti-periplanar to the carbonyl bond. As the lack of overlap of orbitals does not allow the deprotonation within this conformation, amide **8** was unreactive towards TMS-diazomethane.

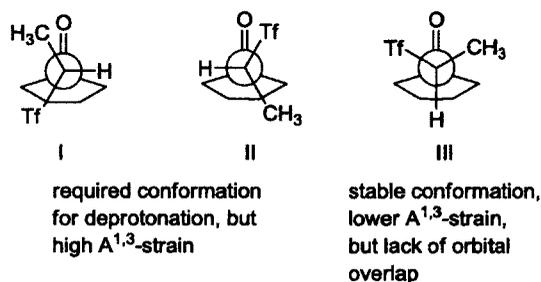
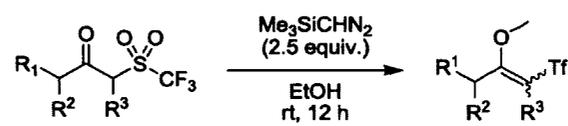


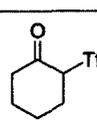
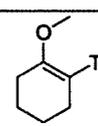
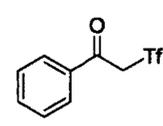
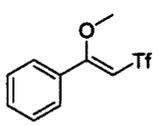
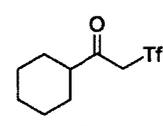
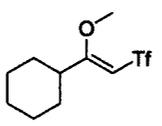
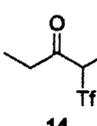
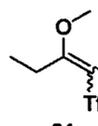
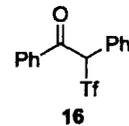
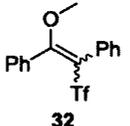
Figure 2. Conformation of 1-(pyrrolidin-1-yl-2-(trifluoromethylsulfonyl))ethanone **8**

2.2.3.3 α -Trifluoromethanesulfonyl Ketones

The α -triflyl ketone substrates were subjected to the methylation under the optimized reaction conditions and resulted in O-methylation akin to α -triflyl amides (Table 7). Unlike amide substrates, some of the ketone substrates afforded a mixture of *E/Z* isomers, and the geometry of alkenes was determined by 2D NOESY spectra analysis.

Table 7. Reaction of Trimethylsilyldiazomethane with α -Triflyl Ketones



Entry	S.M.	Product	Conv. (%) ^a	Yield (%)	<i>Z/E</i> ratio ^b
1	 9	 29	100	66 89 ^c	-
2	 10	 30	100	92	100:0
3	 12	 28	100	68	100:0
4	 14	 31	100	77	25:75
5	 16	 32	82	48	82:18 ^d

^a Determined by integration of the ¹H NMR spectrum of the crude reaction mixture.

^b Assigned via 2D NOESY experiment.

^c 10 equiv. Me₃SiCHN₂, 1 M in MeOH, rt, 3 h.

^d could not be determined which was the major isomers.

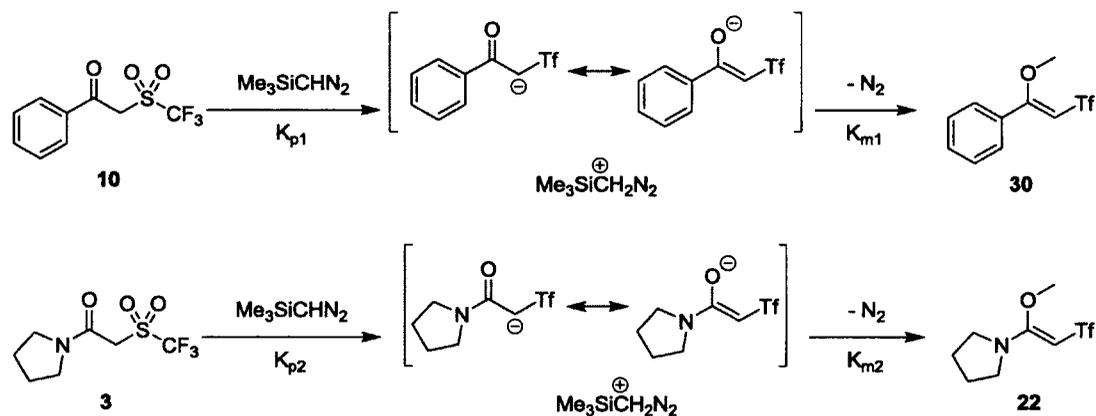
Ketone **10** gave the *Z*-alkene as the only product, as there was no correlation between the methoxy group and methine hydrogen on the α -carbon but there was a correlation between the methine hydrogen and the phenyl group (entry 2) (Appendix B.3.3.4). In contrast to the result with α -substituted amide **8**, α -methyl substituted ketone **14**, 2-triflyl pentan-3-one, was reactive to the methylation, and it afforded the *E/Z* mixture in a 3:1 ratio (entry 4). This selectivity of geometry was not unexpected, given that *E*-isomer is electronically more favored as it minimized the dipole around the alkene, and sterically more favored as alkoxide is bigger than carbon by a chelation with the solvent in the enolate form (Figure 3).³¹ Moreover, this electronic effect allowed the differentiation on TLC and allowed a separation via flash chromatography. Ketone **16**, the most sterically hindered among α -triflyl ketone substrates, was successfully methylated and produced a mixture of *E/Z* isomers. It was not possible to determine which isomer was the major product due to the structure similarity and they were inseparable by chromatography and could not be distinguished by 2D NOESY. It was, however, determined that the ratio between major and minor alkenes was 82:18 based on the ¹H NMR spectrum (entry 5).



Figure 3. Enolate Configuration of Ketone **14**

The mechanism of alkylation with diazomethane has two steps: protonation of diazomethane and nucleophilic attack. We sought to determine the rate limiting step for

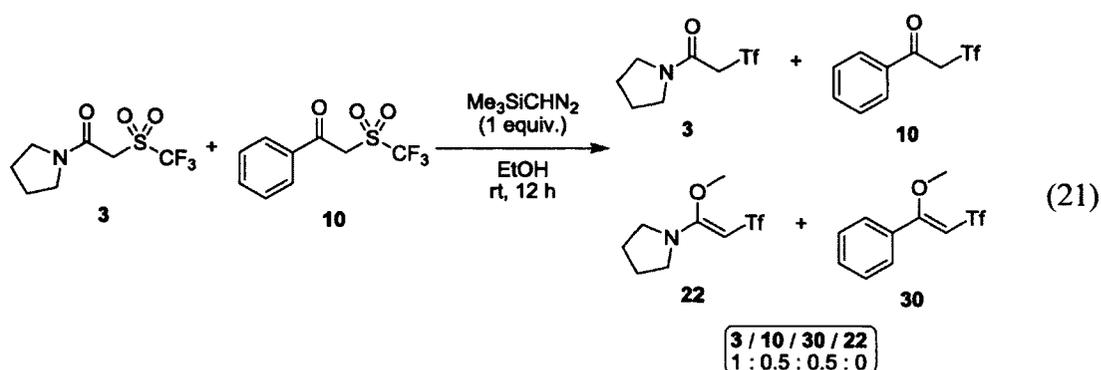
the methylation for our substrates (Scheme 14). Due to the nature of carbonyl groups, ketones are more acidic than amides, thus the rate of protonation of TMS-diazomethane (K_{p1}) with ketone **10** would be faster than with amide **3** (K_{p2}). An amide enolate is a better nucleophile than a ketone enolate, indicating the rate of methylation with an amide (K_{m2}) would be faster than with a ketone (K_{m1}). Thus, if the protonation of diazomethane is the rate limiting step, it would result in the methylation of ketones more than amides. If the methylation is the rate limiting step, it would result in more methylation for amides. In a case where the product is the mixture of both methylated products, it would indicate the rates of protonation and methylation are similar.



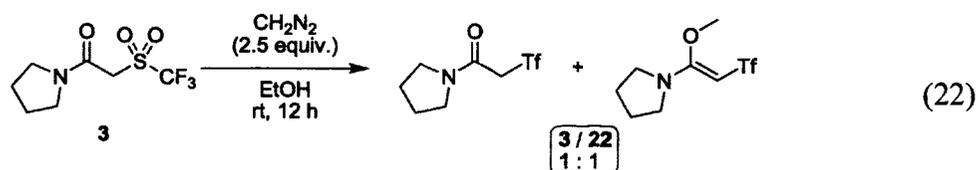
Scheme 14. Reaction Rates of Protonation and Methylation with Ketone and Amide

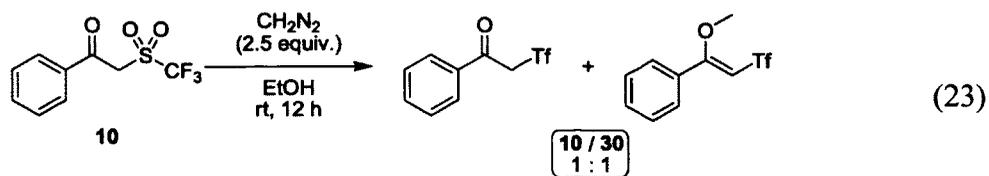
This was explored simply by treating a mixture of amide **3** and ketone **10** with 1 equivalent of TMS-diazomethane (eq 21). After 12 hours, the reaction mixture was concentrated and the ^1H NMR of the crude product was analyzed to show a partial methylation of the ketone. The methoxy peak at 3.82 ppm and the methine hydrogen on the α -carbon at 5.64 ppm were the same as compound **30**. There were not any peaks to

indicate compound **22**; in other words, the amide was completely unreactive. This result supported that the protonation is the rate-limiting step for the reaction of our substrates with TMS-diazomethane.



Even though TMS-diazomethane had a very similar reactivity to diazomethane, the bulky trimethylsilyl group might have an effect on the reaction selectivity. To explore this, a reaction was conducted with freshly prepared diazomethane in ether, 0.43 M calculated from the amount of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) used, on amide **3** and ketone **10** separately. Under the optimized conditions, both reactions gave 50% conversion from crude products (eq 22 and 23). The crude product of eq 23 was charged again with an additional 2.5 equivalent of diazomethane, and the remaining ketone **10** was fully converted into **30** over a further 12 hours, implying the trimethylsilyl moiety of TMS-diazomethane had no effect on the selectivity of the methylation site between enolate oxygen and α -carbon.

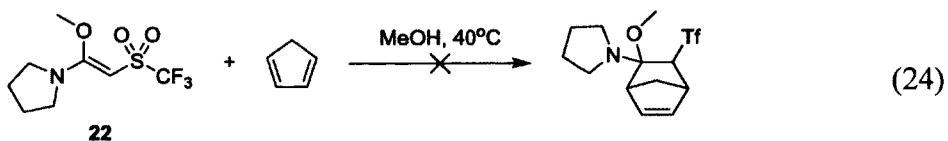


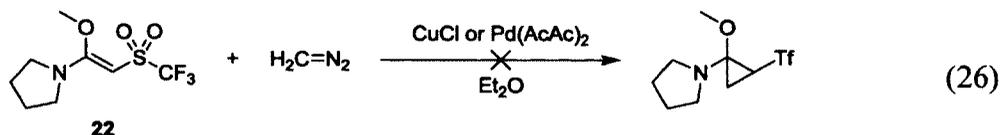
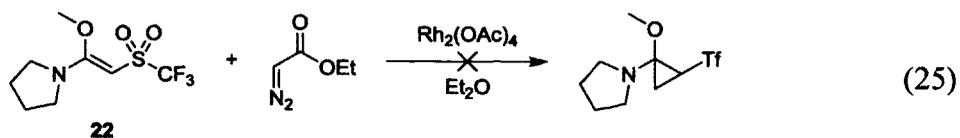


2.2.4 Ambiphilic Alkenes

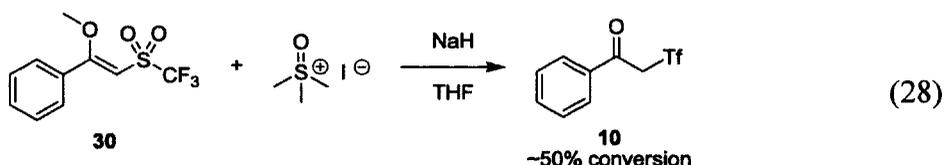
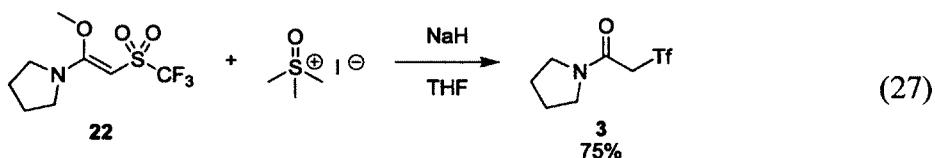
Regardless of the desired alkylation at the α -carbon of α -triflyl carbonyl compounds, the methylation using TMS-diazomethane was predominantly taking place at the enolate oxygen to give ambiphilic alkenes. These vinyl triflone compounds, along with allylic triflones,¹⁸ were not highly studied compared to alkyl or aryl triflones, and the unique properties of ambiphilic alkenes still allowed us to further explore the use of triflones.

As an initial attempt, a Diels-Alder reaction with cyclopentadiene was ventured with alkene **22**. Surprisingly, it was unreactive towards cyclopentadiene at 40 °C, and it still showed no reactivity even when the reaction was performed in the microwave at 150 °C (eq 24). Attempts were also made to perform cyclopropanation to afford a new class of the donor-acceptor cyclopropanes. The cyclopropanation was carried out with ethyl diazoacetate, one of most useful reagents for the preparation of cyclopropane compounds,³² and a quantitative amount of **22** was recovered (eq 25). Then we also attempted cyclopropanation using diazomethane and a metal catalyst. Although gas evolution was observed which indicated the diazomethane was reacting with metals, no desired product was formed (eq 26).



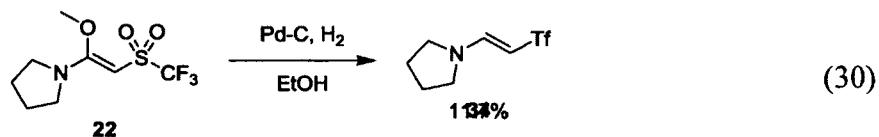
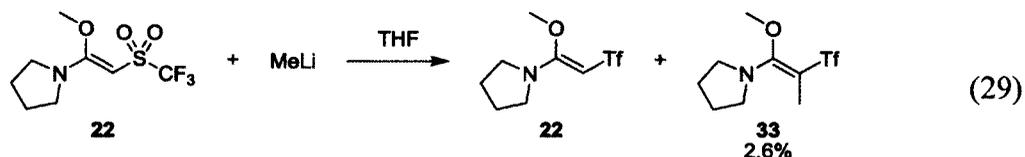


Next, a cyclopropanation using the Corey-Chaykovsky reagent³³ was attempted. Though it is known as a strong reagent, the reaction with alkene **22** had brought an interesting result. Instead of cyclopropanation or methylation, the recovered product from the reaction was amide **3**, confirmed by the ¹H NMR spectrum analysis (eq 27). It was rationalized as the Corey-Chaykovsky reagent was undergoing nucleophilic attack on the carbon of the methoxy, and the rest of molecule acted as leaving group, thus affording amide **3**. This phenomenon was also observed from the reaction on alkene **30**, as confirmed by the ¹H NMR of crude product (eq 28).



After several unsuccessful attempts of the cyclopropanation, we explored other functional group manipulations to illustrate the reactivity of these ambiphilic alkenes. In order to force the reaction, a small and strong nucleophile, methyllithium, was added to a solution of alkene **22**. It was mostly unreactive and resulted in the recovery of alkene **22**, but a very small amount of highly unexpected compound was formed and identified as

compound **33** (eq 29). It was rationalized as the methyllithium deprotonated the vinyl hydrogen and the resulting carbanion underwent a nucleophilic attack on a carbon of the methoxy group of alkene **22**. Also, the hydrogenation using palladium on carbon was attempted to determine if the alkene could be reduced to alkane; even though the full consumption of alkene **22** was monitored by TLC, the obtained product from this hydrogenation was very small amount and also highly unexpected (eq 30).



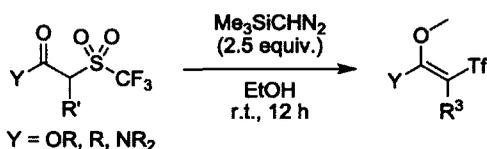
Despite of several attempts to make a use of these ambiphilic alkenes, they had not shown any reactivity towards the cycloaddition or hydrogenation. Moreover, they have given very unexpected and uncontrollable results with other attempts.

2.2.5 Conclusion

To summarize our triflone chemistry, various α -triflyl carbonyl substrates were readily prepared using commercially available sodium trifluoromethanesulfinate (NaTf) with α -bromocarbonyl compounds. The subsequent methylation using TMS-diazomethane was optimized to use 2.5 equivalents in EtOH (1 M) for 12 hours. Despite of our initial goal of C-methylation, the reaction resulted in exclusively in O-methylation for ketone and amide substrates with the good selectivity in the *E/Z* isomers. This O-methylation had led to the formation of ambiphilic alkenes. The rate limiting step of the

methylation was demonstrated to be the protonation of TMS-diazomethane via competition experiments. The hypothesis that the methylation would be driven by HSAB (hard and soft acids and bases) theory rather than electronic effect from strong electron-withdrawing group of triflone was supported by the observed O-methylation.

Table 8. Regioselectivity of Methylation using TMS-diazomethane on α -Triflyl Carbonyl Compounds



Carbonyl Type	C- vs O-methylation	<i>E/Z</i> Selectivity
Ester	non-selective	non-selective
Amide	only O-methylation observed	only <i>Z</i> -alkene observed
Ketone	only O-methylatino observed	substrated dependent

These amphiphilic alkenes were surely interesting and uncommon compounds. Even with great effort, these compounds have not exhibited any reactivities towards the cycloaddition reactions attempted and have resulted in highly unexpected compounds in the hydrogenation and cyclopropanation using the Corey-Chaykovsky reagent.

3 Chapter: Experimental Procedure for Trifluoromethane Sulfones

3.1 General Experimental

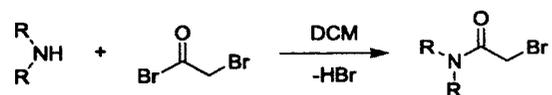
All reagents were purchased from commercial sources such as Sigma-Aldrich, Strem, and TCI, and were used as received without further purification. All non-aqueous reactions were carried out under a positive pressure of dry nitrogen or argon atmosphere. THF was distilled from CaH₂ prior to use. Except as indicated otherwise, reactions were magnetically stirred and monitored by TLC using glass-backed Extra Hard Layer (60 Å) TLC plates from Silicycle and visualized by fluorescence quenching under UV light and/or staining using potassium permanganate or iodine. Flash chromatographic purification of products was performed either on Silia-P Flash silica gel from Silicycle using a forced flow of eluent by the method of Still³⁴ or by automated chromatography on a Biotage Isolera One equipped with a UV detector. Concentration *in vacuo* refers to rotary evaporation at 40 °C under the appropriate pressure. Yields refer to purified and spectroscopically pure compounds unless explicitly indicated as crude.

NMR spectra were recorded on Bruker Avance III 300 or Bruker AMX 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as internal standard for ¹H and ¹³C NMR spectra. ¹⁹F NMR spectra are referenced to α,α,α-trifluorotoluene (-63.7 ppm). IR spectra were recorded on a Varian 1000 Scimitar Series. Absorptions are given in wavenumbers (cm⁻¹). High-resolution mass spectrometry was conducted using an ABI Sciex QSTAR XL electrospray quadrupole-time-of-flight (ESI-QTOF) spectrometer with cesium iodide as an internal reference, or on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV at the Ottawa-Carleton Mass Spectrometry Center.

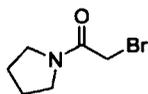
3.2 Synthesis of α -Trifluoromethanesulfone Amides

3.2.1 Synthesis of α -Bromoamide

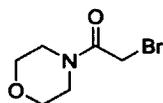
General procedure of α -Bromoamide



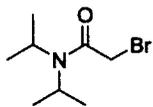
Amine (2.0 equiv.) was added to stirred solution of bromoacetyl bromide (1.0 equiv.) in DCM (ca. 0.15 M) at 0 °C. After 30 min, reaction was warmed to room temperature, stirred for 1 h, and saturated ammonium chloride solution was added. The mixture was extracted with Et₂O (2 x), dried over anhydrous Na₂SO₄, filtered, and concentrated to dryness. No further purification was required.



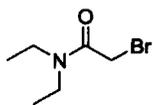
Prepared according to the general procedure using pyrrolidine (2.88 mL, 35.54 mmol, 2.0 equiv.) and bromoacetyl bromide (1.50 mL, 17.27 mmol, 1.0 equiv.) to afford 2-bromo-1-(pyrrolidin-1-yl)ethanone (3.05 g, 15.89 mmol, 92%) as a yellow solid.³⁵ ¹H NMR (CDCl₃, 300 MHz): δ 1.87-2.08 (m, 4H), 3.50-3.58 (m, 4H), 3.83 (s, 2H).



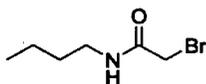
Prepared according to the general procedure using morpholine (1.00 mL, 11.51 mmol, 2.0 equiv.) and bromoacetyl bromide (0.50 mL, 5.76 mmol, 1.0 equiv.) to afford 2-bromo-1-morpholinoethanone (1.23 g, 5.91 mmol, 100%) as a colorless oil.³⁶ ¹H NMR (CDCl₃, 300 MHz): δ 3.53-3.56 (m, 2H), 3.64-3.78 (m, 6H), 3.87 (s, 2H).



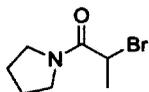
Prepared according to the general procedure using diisopropylamine (5.10 mL, 36.27 mmol, 2.0 equiv.) and bromoacetyl bromide (1.50 mL, 17.27 mmol, 1.0 equiv.) to afford 2-bromo-*N,N*-diisopropylacetamide (3.88 g, 17.45 mmol, 100%) as a yellow oil.³⁷ ¹H NMR (CDCl₃, 300 MHz): δ 1.27 (d, *J* = 6.6 Hz, 6H), 1.41 (d, *J* = 6.9 Hz, 6H), 3.40-3.51 (m, 1H), 3.83 (s, 2H), 3.90-4.04 (m, 1H).



Prepared according to the general procedure using diethylamine (3.75 mL, 36.26 mmol, 2.0 equiv.) and bromoacetyl bromide (1.50 mL, 17.27 mmol, 1.0 equiv.) to afford 2-bromo-*N,N*-diethylacetamide (3.49 g, 14.12 mmol, 81%) as an orange oil.³⁸ ¹H NMR (CDCl₃, 300 MHz): δ 1.14 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 3.39 (dq, *J* = 1.3, 7.2 Hz, 4H), 3.85 (s, 2H).

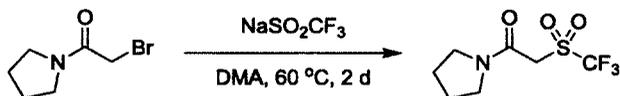


Prepared according to the general procedure using *n*-butylamine (2.41 mL, 24.18 mmol, 2.0 equiv.) and bromoacetyl bromide (1.00 mL, 11.51 mmol, 1.0 equiv.) to afford 2-bromo-*N*-butylacetamide (2.15 g, 11.08 mmol, 96%) as a white solid.³⁹ ¹H NMR (CDCl₃, 400 MHz): δ 0.96 (t, *J* = 5.7 Hz, 3H), 1.34-1.44 (m, 2H), 1.51-1.61 (m, 2H), 3.29-3.34 (m, 2H), 3.91 (s, 2H).



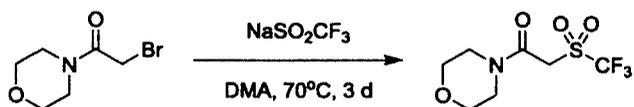
Prepared according to the general procedure using pyrrolidine (1.00 mL, 11.99 mmol, 2.0 equiv.) and bromoacetyl bromide (0.63 mL, 6.01 mmol, 1.0 equiv.) to afford 2-bromo-1-(pyrrolidin-1-yl)propan-1-one (1.14 g, 5.53 mmol, 92%) as a greenish liquid. IR (NaCl plate): ν 1650, 1450, 1431. ^1H NMR (CDCl_3 , 300 MHz): δ 1.93 (d, $J = 6.6$ Hz, 3H), 1.8-2.1 (m, 4H), 3.35-3.52 (m, 3H), 3.65-3.72 (m, 1H), 4.46 (q, $J = 6.7$ Hz, 1H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.34, 24.22, 26.10, 40.39, 46.46, 46.51, 167.54. HRMS: m/z calcd for $\text{C}_7\text{H}_{12}\text{N}_1\text{O}_1\text{Br}$: 205.0102; found: 205.0150.

3.2.2 Synthesis of α -Triflyl Amide

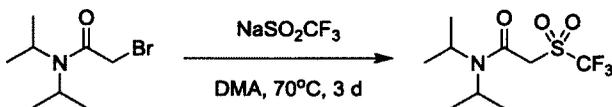


Three parallel reactions were performed using 2-bromo-1-(pyrrolidin-1-yl)ethanone (500 mg, 2.60 mmol, 1.0 equiv.) and sodium trifluoromethanesulfinate (600 mg, 3.86 mmol, 1.5 equiv) in stirring DMA (2.6 mL) at 60 °C under N_2 . After 2 days, each reaction was cooled to rt, diluted with ether (20 mL), individually filtered over Celite, and concentrated to dryness. The resulting mixtures were combined and purified by flash chromatography (350 g of silica, 40% EtOAc/hex + 1% pyridine additive) to afford 1-(pyrrolidin-1-yl)-2-(trifluoromethanesulfonyl)ethanone **3** (1.72 g, 7.01 mmol, 90%) as a pale yellow solid. R_f (40% EtOAc/hex): 0.20. IR (NaCl plate): ν 1665, 1649, 1364, 1219, 1190, 1118, 781. ^1H NMR (CDCl_3 , 400 MHz): δ 1.92-2.09 (m, 4H), 3.55-3.64 (m, 4H), 4.31 (s, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 24.36, 26.03, 46.79, 47.91, 55.08, 119.20 (q,

$J = 327$ Hz), 156.20. ^{19}F NMR (CDCl_3 , 376 MHz): δ -75.84. HRMS (ESI-QTOF): m/z $[\text{M} + \text{H}^+]$ calcd for $\text{C}_7\text{H}_{10}\text{F}_3\text{NO}_3\text{S} + \text{H}$: 246.0412; found: 246.0408.

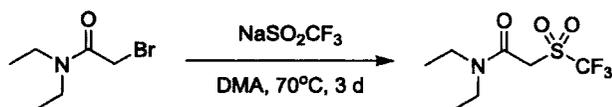


2-bromo-1-morpholinoethanone (202 mg, 0.97 mmol, 1.0 equiv.) and sodium trifluoromethanesulfinate (311 mg, 1.94 mmol, 2.0 equiv.) were dissolved in DMA (2 mL), and the mixture was stirred for 3 days at 70 °C under N_2 . The reaction was cooled to 60 °C, concentrated to dryness, diluted with ether, filtered over Celite, and concentrated to dryness again. The resulting residue was purified by automated flash chromatography (10 g silica column, 50% EtOAc/hex) to afford 2-(trifluoromethanesulfonyl)-1-morpholinoethanone **4** (133 mg, 0.51 mmol, 52%) as a white solid. R_f (30% EtOAc/hex): 0.08. IR (NaCl plate): ν 1640, 1363, 1223, 1197, 1126, 779. ^1H NMR (CDCl_3 , 400 MHz): δ 3.58-3.59 (m, 2H), 3.73-3.80 (m, 6H), 3.38 (s, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 43.12, 47.61, 53.30, 66.42, 66.47, 119.16 (q, $J = 327$ Hz), 156.49. ^{19}F NMR (CDCl_3 , 376 MHz): δ -75.85. HRMS (ESI-QTOF): m/z $[\text{M} + \text{Na}^+]$ calcd for $\text{C}_7\text{H}_{10}\text{F}_3\text{NO}_4\text{S} + \text{Na}$: 284.0180; found: 284.0181

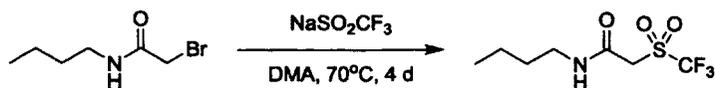


2-bromo-*N,N*-diisopropylacetamide (1.02 g, 4.60 mmol, 1.0 equiv.) and sodium trifluoromethanesulfinate (1.08 g, 6.92 mmol, 1.5 equiv.) were dissolved in DMA (9.5 mL) and stirred for 3 days at 70 °C under N_2 . The reaction was cooled to 60 °C and concentrated under vacuum. The resulting residue was flushed through silica (50%

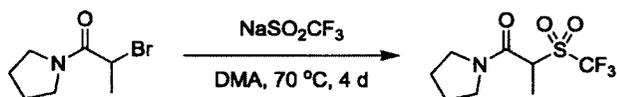
EtOAc/hex) to afford *N,N*-diisopropyl-2-(trifluoromethanesulfonyl)acetamide **5** (680 mg, 2.47 mmol, 54%) as a yellow solid. R_f (20% EtOAc/hex): 0.36. IR (NaCl plate): ν 1645, 1381, 1360, 1343, 1194, 1120, 771. ^1H NMR (CDCl_3 , 300 MHz): δ 1.30 (d, $J = 6.9$ Hz, 6H), 1.43 (d, $J = 6.6$ Hz, 6H), 3.57 (septet, $J = 6.8$ Hz, 1H), 3.95 (septet, $J = 6.6$ Hz, 1H), 4.35 (s, 2H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 20.02, 20.83, 47.22, 51.19, 55.59, 119.23 (q, $J = 327$ Hz), 156.58. ^{19}F NMR (CDCl_3 , 282 MHz): δ -75.67. HRMS (ESI-QTOF): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_9\text{H}_{16}\text{F}_3\text{NO}_3\text{S} + \text{Na}$: 298.0701; found: 298.0697.



2-bromo-*N,N*-diethylacetamide (1.01 g, 5.18 mmol, 1.0 equiv.) and sodium trifluoromethanesulfinate (1.21 g, 7.74 mmol, 1.5 equiv.) were dissolved in DMA (10 mL), and stirred for 3 days at 70 °C under N₂. The reaction was cooled to 60 °C and concentrated under vacuum. The resulting residue was flushed through silica (50% EtOAc/hex) to afford *N,N*-diethyl-2-(trifluoromethanesulfonyl)acetamide **6** (1.09 g, 4.42 mmol, 86%) as a yellow solid. R_f (20% EtOAc/hex): 0.20. IR (NaCl plate): ν 1654, 1369, 1211, 1120, 771. ^1H NMR (CDCl_3 , 300 MHz): δ 1.19 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 3.44 (q, $J = 7.3$ Hz, 2 H), 3.47 (q, $J = 7.2$ Hz, 2 H), (m, 4H), 4.35 (s, 2H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 12.61, 14.27, 41.16, 43.34, 53.91, 119.22 (q, $J = 327$ Hz), 157.39. ^{19}F NMR (CDCl_3 , 282 MHz): δ -75.43. HRMS (ESI-QTOF): m/z [$\text{M} + \text{H}^+$] calcd for $\text{C}_7\text{H}_{12}\text{F}_3\text{NO}_3\text{S} + \text{H}$: 248.0568; found: 248.0562.



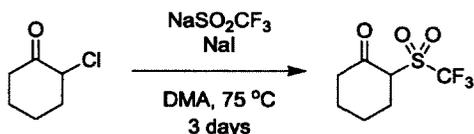
2-bromo-*N*-butylacetamide (582 mg, 3.05 mmol, 1.0 equiv.) and sodium trifluoromethanesulfinate (562 mg, 3.67 mmol, 1.2 equiv.) were dissolved in DMA (3 mL). The mixture was stirred for 2 days at 70 °C, and then more sodium trifluoromethanesulfinate (240 mg, 1.50 mmol, 0.5 equiv.) was added and stirred for additional 2 days. The reaction was quenched with H₂O (3 mL), extracted with ether (3 x 5 mL), dried over anhydrous Na₂SO₄, and concentrated to dryness. The resulting residue was flushed through silica (30% EtOAc/hex) to afford *N*-butyl-2-(trifluoromethanesulfonyl)acetamide **7** (527 mg, 2.13 mmol, 71%) as a white solid. *R_f* (20% EtOAc/hex): 0.19. IR (NaCl plate): ν 3348, 1668, 1541, 1348, 1223, 1197, 1126, 723. ¹H NMR (CDCl₃, 400 MHz): δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.34-1.44 (m, 2H), 1.53-1.60 (m, 2H), 3.37 (dt, *J* = 4.5 Hz, 0.75 Hz, 2H), 4.13 (s, 2H), 6.34 (broad, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 13.59, 19.86, 31.08, 40.34, 55.09, 119.20 (q, *J* = 327 Hz), 156.88. ¹⁹F NMR (CDCl₃, 376 MHz): δ -75.89. HRMS (ESI-QTOF): *m/z* [M + H⁺] calcd for C₇H₁₂F₃NO₃S + H: 248.0568; found: 248.0570.



2-bromo-1-(pyrrolidin-1-yl)propan-1-one (199 mg, 0.97 mmol, 1.0 equiv.) and sodium trifluoromethanesulfinate (232 mg, 1.49 mmol, 1.5 equiv.) were dissolved in DMA (1 mL) and stirred at 70 °C under N₂ for 2 days. And then, more sodium trifluoromethanesulfinate (130 mg, 0.83 mmol, 0.8 equiv.) was added and stirred for additional 2 days. The reaction was cooled to 60 °C and concentrated under vacuum. The

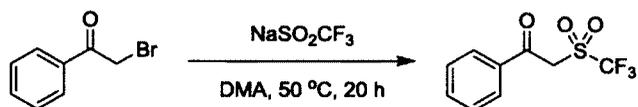
resulting residue was dissolved in Et₂O, filtered over Celite, concentrated, and purified by automated flash chromatography (25 g silica column, 30% EtOAc/hex) to afford pyrrolidyl-2-(trifluoromethanesulfonyl)propylamide **8** (105 mg, 0.40 mmol, 86%) as a yellow solid. *R_f* (30% EtOAc/hex): 0.17. IR (NaCl plate): ν 1650, 1355, 1203, 1189, 1119, 702. ¹H NMR (CDCl₃, 400 MHz): δ 1.78 (d, *J* = 7.2 Hz, 3H), 1.75-2.30 (m, 4H), 3.45-3.66 (m, 3H), 3.75-3.81 (m, 1H), 4.43 (q, *J* = 6.9 Hz, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ 12.80, 24.27, 26.00, 46.96, 47.37, 60.41, 119.73 (q, *J* = 329 Hz), 160.07. ¹⁹F NMR (CDCl₃, 376 MHz): δ -73.41. HRMS (ESI-QTOF): *m/z* [M + H⁺] calcd for C₈H₁₂F₃NO₃S + H: 260.0568; found: 260.0568.

3.3 Synthesis of α -Triflyl Ketones

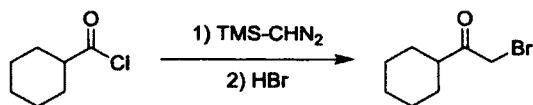


To a solution of 2-chlorocyclohexanone (332 mg, 2.50 mmol, 1.0 equiv.) and sodium iodide (561 mg, 3.75 mmol, 1.5 equiv.) in DMA (2.5 mL) was added sodium trifluoromethanesulfinate (780 mg, 5.0 mmol, 2.0 equiv.) and the resulting mixture was stirred at 75°C for 3 days. The reaction was quenched with distilled water (5 mL), extracted with ether (3 x 10 mL), and combined organic layers were washed with H₂O (10 mL) and brine (10 mL), and dried over anhydrous MgSO₄, filtered, concentrated to dryness, and purified by automated flash chromatography (50 g silica column, 5% EtOAc/hex) to afford 2-(trifluoromethanesulfonyl)cyclohexanone **9** (250 mg, 1.07 mmol, 43%) as a yellow oil.⁴⁰ *R_f* (20% EtOAc/hex): 0.40. IR (NaCl plate): ν 1728, 1604, 1367, 1204, 1115. ¹H NMR (CDCl₃, 300 MHz): δ 1.75 – 2.86 (m, 8H–ketone/8H–enol), 4.11 –

4.15 (m, 1H–ketone), 9.84 (s, 1H–enol); ^{13}C NMR (CDCl_3 , 75 MHz): δ 21.34, 22.13, 22.31, 23.21, 26.25, 27.01, 30.28, 41.40, 68.32, 96.32, 119 (q, $J = 328$ Hz), 120 (q, $J = 327$ Hz), 174.39, 199.00. ^{19}F NMR (CDCl_3 , 282 MHz): δ -77.43 (enol), -73.71 (ketone).

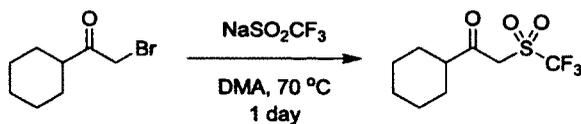


To a solution of 2-bromoacetophenone **11** (1.04 g, 5.02 mmol, 1.0 equiv.) in DMA (5.53 mL) was added sodium trifluoromethanesulfinate (863 mg, 5.53 mmol, 1.1 equiv.), and the mixture was stirred at 50 °C for 20 hours under N₂. The reaction was quenched with H₂O (30 mL), extracted with Et₂O (2 x 30 mL). Combined organic layers were washed with water (15 mL), dried over anhydrous Na₂SO₄, concentrated to dryness to give crude yellow oil that was flushed through silica (20% EtOAc/hex). The resulting solution was concentrated to dryness and purified by automated flash chromatography (100 g silica, 5-10% EtOAc/hex) to afford 1-phenyl-2-(trifluoromethanesulfonyl)ethanone **10** (1.00 g, 3.96 mmol, 79%) as a yellow solid.⁴¹ R_f (10% EtOAc/hex): 0.14. IR (NaCl plate): ν 1688, 1372, 1208, 1117, 740. ^1H NMR (CDCl_3 , 300 MHz): δ 4.87 (s, 2H–ketone), 5.81 (s, 1H–enol), 7.55–7.60 (m, 2H), 7.70–7.75 (m, 1H), 7.98–8.01 (m, 2H), 10.41 (s, 1H–enol). ^{13}C NMR (CDCl_3 , 75 MHz): δ 55.80, 119.20 (q, $J = 327$ Hz), 129.21, 129.23, 135.25, 184.56. ^{19}F NMR (CDCl_3 , 282 MHz): δ -97.22 (enol), -75.74 (ketone). HRMS (ESI-QTOF): m/z [M + Na⁺] calcd for C₉H₇F₃O₃S + Na: 174.9966; found: 274.9965.

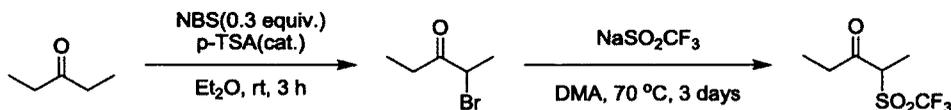


Me₃SiCHN₂ (2.0 M in Et₂O, 5 mL, 10 mmol, 2.0 equiv.) was added to a stirred solution of cyclohexanecarbonyl chloride (733 mg, 5.0 mmol, 1.0 equiv.) in a mixture of THF (10 mL) and acetonitrile (10 mL) at 0 °C under N₂. The mixture was allowed to warm to rt and be stirred overnight. It was washed with saturated NH₄Cl solution (15 mL), saturated NaHCO₃ solution (15 mL), and brine (15 mL), and dried over anhydrous Na₂SO₄, filtered and concentrated to dryness. The resulting bright yellow liquid was purified by flash chromatography (10% EtOAc/hex) to afford cyclohexyldiazomethylketone (625 mg, 4.11 mmol, 82%). ¹H NMR (CDCl₃, 300 MHz): δ 1.15-1.53 (m, 5H), 1.60-1.95 (m, 5H), 2.15-2.35 (m, 1H), 5.27 (s, 1H).

The obtained cyclohexyl diazomethyl ketone was dissolved in hexanes (8.2 mL), and HBr (0.69 mL of 48% aqueous HBr solution, 6.16 mmol of HBr, 1.5 equiv.) was added slowly, and vigorous bubbling was observed. After solution was stirred at rt for 2 h, saturated NaHCO₃ solution (5 mL) was added and the mixture was stirred for an additional 5 min, washed with H₂O (3 x 10 mL), and dried over anhydrous Na₂SO₄. Filtration and concentration gave pure 2-bromo-1-cyclohexylethanone **11** (660 mg, 3.23 mmol, 78%), as a pale yellow liquid. ¹H NMR (CDCl₃, 300 MHz): δ 1.15-1.55 (m, 5H), 1.65-1.98 (m, 5H), 2.68-2.80 (m, 1H), 3.99 (s, 2H).



2-bromo-1-cyclohexylethanone **11** (660 mg, 3.23 mmol, 1.0 equiv.) and sodium trifluoromethanesulfinate (755 mg, 4.84 mmol, 1.5 equiv.) were dissolved in DMA (3.23 mL) and stirred at 70 °C under N₂ for 24 hours. The reaction was quenched with H₂O (10 mL), and extracted with ether (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over anhydrous Na₂SO₄. Filtration and concentration gave a reddish solid that was triturated with hexanes and the resulting yellow/green solid was dissolved in 20% EtOAc/hex, flushed through silica, concentrated to dryness to afford 1-cyclohexyl-2-(trifluoromethanesulfonyl)ethanone **12** (520 mg, 2.01 mmol, 63%) as a white solid. *R_f* (20% EtOAc/hex): 0.59. IR (NaCl plate): ν 1723, 1359, 1208, 1195, 1115, 711. ¹H NMR (CDCl₃, 300 MHz): δ 1.16-1.47 (m, 5H-ketone/5H-enol), 1.69-1.98 (m, 5H-ketone/5H-enol), 2.60-2.70 (m, 1H-ketone), 4.33 (s, 2H-ketone), 5.19 (s, 1H-enol), 10.10 (s, 1H-enol). ¹³C NMR (CDCl₃, 75 MHz): δ 25.17, 25.45, 27.80, 45.19, 51.81, 57.92, 84.03, 119.07 (q, *J* = 327 Hz), 185.73, 197.54. ¹⁹F NMR (CDCl₃, 282 MHz): δ -79.67 (enol), -76.05 (ketone). HRMS (ESI-QTOF): *m/z* [M - H⁺] calcd for C₉H₁₃F₃O₃S - H: 257.0459; found: 257.0491.



3-pentanone (1.06 mL, 10.00 mmol, 1.0 equiv.), NBS (534 mg, 3.00 mmol, 0.3 equiv.), and p-TSA (190 mg, 1.00 mmol, 0.1 equiv.) were dissolved in ether (10 mL). The mixture was stirred for 3 hours at rt, quenched with H₂O (10 mL), extracted ether (3 x 10 mL).

Combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over anhydrous Na₂SO₄, filtered, and partially concentrated at atmospheric pressure at 55-60 °C. Succinimide was removed by filtration through silica (30% Et₂O/pentanes). The mixture was partially concentrated to *ca.* 5-10 mL, combined with sodium trifluoromethanesulfinate (940 mg, 6.00mmol, 0.6 equiv.) and DMA (3 mL), then stirred at 70 °C under N₂ for 3 days. The reaction was quenched with H₂O (3 mL), and extracted with Et₂O (3 x 10 mL). Combined organic layers were washed with H₂O (10 mL), brine (10 mL), dried over anhydrous Na₂SO₄, filtered, concentrated to dryness. The resulting residue was flushed through silica (20% EtOAc/hex) and concentrated to dryness to afford 2-(trifluoromethanesulfonyl)pentan-3-one **14** (67 mg, 0.31 mmol, 100% with respect to NBS) as a orange oil. *R_f* (10% EtOAc/hex): 0.24. IR (NaCl plate): ν 1731, 1364, 1209, 1123, 701. ¹H NMR (CDCl₃, 300 MHz): δ 1.56 (t, *J* = 6.9 Hz, 3H), 1.69-1.72 (dd, *J* = 0.9 Hz, 7.2 Hz, 3H), 2.70 (dq, *J* = 7.1 Hz, 19.0 Hz, 1H), 2.92 (dq, *J* = 7.2 Hz, 19.1 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 1H). ¹³C NMR (CDCl₃, 75 MHz): δ 7.36, 11.22, 36.75, 65.85, 119.55 (q, *J* = 329 Hz), 198.97. ¹⁹F NMR (CDCl₃, 282 MHz): δ -73.30. HRMS: *m/z* calcd C₆H₉O₃S₁F₃ for: 218.0226; found: 218.0235.



Deoxybezoin (1.96 g, 10.00 mmol, 1.0 equiv.), NBS (1.96 g, 11.00 mmol, 1.1 equiv.), and p-TSA (190 mg, 1.00 mmol, 0.1 equiv.) were combined and heated to 80°C to melt the solids. After stirring for 10 min, the mixture was allowed to cool for 5 min, and quenched with H₂O (20 mL), extracted with TBME (20 mL). The organic phase was

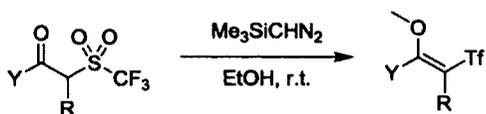
washed with brine (20 mL), H₂O (20 mL), dried over anhydrous Na₂SO₄, and concentrated to dryness to afford crude 2-bromo-1,2-diphenylethanone **15** (2.78 g, 10.11 mmol, 92%) as a yellow oil. *R_f* (% EtOAc/hex): 0.24. IR (NaCl plate): ν 1690. ¹H NMR (CDCl₃, 300 MHz): δ 6.40 (s, 1H), 7.33-7.42 (m, 3H), 7.45-7.49 (m, 2H), 7.53-7.60 (m, 3H), 8.00-8.02 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 51.04, 128.82, 129.04, 129.15, 133.72, 134.17, 135.91

2-bromo-1,2-diphenylethanone (300 mg, 1.09 mmol, 1.0 equiv.) and sodium trifluoromethanesulfinate (340 mg, 2.18 mmol, 2.0 equiv.) were dissolved in DMA (1.1 mL) and stirred at 70 °C under N₂ for 3 days. The reaction was quenched with water (2 mL), extracted with ether (3 x 5 mL). The combined organic layers were washed with H₂O (10 mL), brine (10 mL), and dried over anhydrous Na₂SO₄, filtered, concentrated to dryness. The resulting residue was purified by automated flash chromatography (25 g silica column, 10% EtOAc/hex) to afford 1,2-diphenyl-2-(trifluoromethanesulfonyl)ethanone **16** (120 mg, 0.37 mmol, 34%) as a white solid. *R_f* (10% EtOAc/hex): 0.48. IR (NaCl plate): ν 1686, 1370, 1208, 1113, 768. ¹H NMR (CDCl₃, 300 MHz): δ 5.98 (s, 1H-enol), 6.36 (s, 1H-ketone), 7.40-7.55 (m, 10H), 7.55-7.70 (m, 6H), 7.85-8.00 (m, 4H). ¹³C NMR (CDCl₃, 75 MHz): δ 72.39, 72.40, 76.22, 119.77 (q, *J* = 330 Hz), 129.00, 129.16, 129.73, 130.76, 130.85, 134.79, 187.49, 198.99. ¹⁹F NMR (CDCl₃, 282 MHz): δ -75.12 (enol), -71.91 (ketone). HRMS (ESI-QTOF): *m/z* [M + Na⁺] calcd for C₁₅H₁₁F₃O₃S + Na: 351.0279; found: 351.0308.

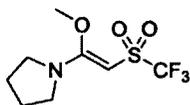
3.4 Reaction with Trimethylsilyldiazomethane with α -Trifluoromethanesulfone

Carbonyl Compounds

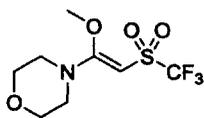
General Procedure



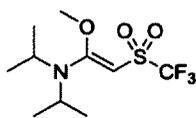
To a solution of α -triflyl carbonyl compound in ethanol (0.5 M) was added $\text{Me}_3\text{SiCHN}_2$ (2.5 equiv.) slowly and stirred at room temperature. Reaction mixture was concentrated under reduced pressure and purified by flash chromatography to afford corresponding product.



1-(pyrrolidin-1-yl)-2-(trifluoromethanesulfonyl)ethanone **3** (112 mg, 0.47 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure and the resulting material was purified by flash chromatography (35 g silica, 2 cm diameter column, 30% EtOAc/hex + 1% pyridine additive) to afford (Z)-1-(1-methoxy-2-(trifluoromethanesulfonyl)vinyl)pyrrolidine **22** (88 mg, 0.34 mmol, 74%) as a yellow solid. R_f (30% EtOAc/hex): 0.17. IR (NaCl plate): ν 1561, 1477, 1401, 1333, 1201, 1171, 1117, 728. ^1H NMR (CDCl_3 , 400 MHz): δ 2.00-2.03 (m, 4H), 3.43-3.47 (m, 4H), 3.98 (s, 3H), 4.14 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 25.11, 48.28, 62.15, 67.22, 120.72 (q, $J = 326$ Hz). ^{19}F NMR (CDCl_3 , 376 MHz): δ -79.21. HRMS (ESI-QTOF): m/z [$\text{M} + \text{H}^+$] calcd for $\text{C}_8\text{H}_{12}\text{F}_3\text{NO}_3\text{S} + \text{H}$: 260.0568; found: 260.0547.

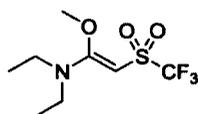


1-morpholino-2-(trifluoromethanesulfonyl)ethanone **4** (40 mg, 0.15 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure and the resulting material was purified by the automated flash chromatography (10 g silica column, 30% EtOAc/hex) to afford (Z)-4-(1-methoxy-2-(trifluoromethanesulfonyl)vinyl)morpholine **23** (34 mg, 0.12 mmol, 81%) as a yellow oil. R_f (30% EtOAc/hex): 0.11. IR (NaCl plate): ν 1563, 1200, 1115. ^1H NMR (CDCl_3 , 400 MHz): δ 3.44-3.47 (m, 4H), 3.75-3.77 (m, 4H), 3.93 (s, 3H), 4.29 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 29.70, 47.85, 61.66, 66.05, 120.50 (q, $J = 325$ Hz), 169.88. ^{19}F NMR (CDCl_3 , 376 MHz): δ -79.09. HRMS (ESI-QTOF): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_8\text{H}_{12}\text{F}_3\text{NO}_3\text{S} + \text{Na}$: 298.0387; found: 297.0337.

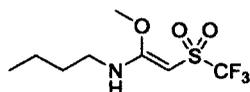


N,N-diisopropyl-2-(trifluoromethanesulfonyl)acetamide **5** (51 mg, 0.18 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure, but for 2 days, and the resulting material was purified by the flash chromatography (10 g silica, 1 cm diameter, 30% ether/hex) to afford (Z)-*N*-isopropyl-*N*-(1-methoxy-2-(trifluoromethanesulfonyl)vinyl)propan-2-amine **24** (12 mg, 0.04 mmol, 23%) as a yellow solid. R_f (50% DCM/hex): 0.34. IR (NaCl plate): ν 1576, 1353, 1334, 1185, 706. ^1H NMR (CDCl_3 , 400 MHz): δ 1.30 (d, $J = 3.8$ Hz, 12H), 3.88-3.95 (m, 2H), 4.05 (s, 1H), 4.12 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.14, 49.85, 63.53, 64.33, 120.86 (q, $J =$

326 Hz), 171.19. ^{19}F NMR (CDCl_3 , 376 MHz): δ -79.31. HRMS (ESI-QTOF): m/z [$\text{M} + \text{H}^+$] calcd for $\text{C}_{10}\text{H}_{18}\text{F}_3\text{NO}_3\text{S} + \text{H}$: 290.1038; found: 290.1032

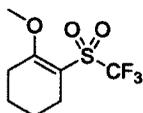


N,N-diethyl-2-(trifluoromethanesulfonyl)acetamide **6** (52 mg, 0.21 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure, but for 18 hours, and the resulting material was purified by the flash chromatography (10 g silica, 1 cm diameter column, 50% DCM/hex) to afford (*Z*)-*N,N*-diethyl-1-methoxy-2-(trifluoromethanesulfonyl)ethenamine **25** (24 mg, 0.09 mmol, 44%) as a yellow oil. R_f (50% DCM/hex): 0.22. IR (NaCl plate): ν 1562, 1327, 1205, 1179, 1122. ^1H NMR (CDCl_3 , 400 MHz): δ 1.24 (t, $J = 7.2$ Hz, 6H), 3.34 (q, $J = 7.2$, 4H), 4.03 (s, 3H), 4.23 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 12.63, 43.37, 64.18, 67.12, 120.73 (q, $J = 326$ Hz), 169.78. ^{19}F NMR (CDCl_3 , 376 MHz): δ -79.31. HRMS (ESI-QTOF): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_8\text{H}_{14}\text{F}_3\text{NO}_3\text{S} + \text{Na}$: 284.0544; found: 284.0554.

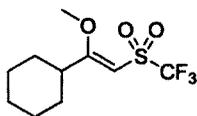


N-butyl-2-(trifluoromethanesulfonyl)acetamide **7** (39 mg, 0.16 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure, but for 2.5 days, and the resulting material was purified by the automated flash chromatography (10 g silica column, 5-10% EtOAc/hex) to afford (*Z*)-*N*-(1-methoxy-2-(trifluoromethanesulfonyl)vinyl)butan-1-amine **26** (10 mg, 0.04 mmol, 23%) as a yellow oil. R_f (10% EtOAc/hex): 0.31. IR (NaCl plate): ν 3373, 1608, 1501, 1412, 1327, 1202, 1181, 1101, 713. ^1H NMR (CDCl_3 , 400

MHz): δ 80.94 (t, $J = 7.6$ Hz, 3H), 1.33-1.40 (m, 2H), 1.48-1.55 (m, 2H), 3.24 (q, $J = 5.0$ Hz, 2H), 3.86 (s, 3H), 4.06 (s, 1H), 7.14 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 13.59, 19.74, 31.54, 40.61, 56.70, 57.38, 57.39, 120.87 (q, $J = 325$ Hz), 168.17. ^{19}F NMR (CDCl_3 , 282 MHz): δ -80.54. HRMS (ESI-QTOF): m/z [$\text{M} + \text{H}^+$] calcd for $\text{C}_8\text{H}_{14}\text{F}_3\text{NO}_3\text{S} + \text{H}$: 262.0725; found: 262.0722.

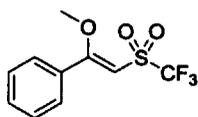


2-(trifluoromethanesulfonyl)cyclohexanone **9** (46 mg, 0.20 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure and the resulting material was purified by automated flash chromatography (10 g silica column, 10-20% EtOAc/hex) to afford 1-methoxy-2-(trifluoromethanesulfonyl)cyclohex-1-ene **29** (32 mg, 0.13 mmol, 66%) as a yellow oil. R_f (30% EtOAc/hex): 0.43. IR (NaCl plate): ν 1604, 1374, 1357, 1247, 1206, 1195, 1151, 1120, 759. ^1H NMR (CDCl_3 , 400 MHz): δ 1.69-1.82 (m, 4H), 2.47-2.48 (m, 4H), 3.83 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 21.62, 22.15, 24.83, 26.29, 55.48, 106.16, 120.39 (q, $J = 328$ Hz), 171.49. ^{19}F NMR (CDCl_3 , 376 MHz): δ -77.01. HRMS (ESI-QTOF): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_8\text{H}_{11}\text{F}_3\text{O}_3\text{S} + \text{Na}$: 267.0279; found: 267.0283.

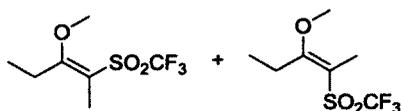


1-cyclohexyl-2-(trifluoromethanesulfonyl)ethanone **12** (43 mg, 0.16 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure and the resulting material was purified by automated flash chromatography (10 g silica, 0-10% EtOAc/hex) to afford

(Z)-(1-methoxy-2-(trifluoromethanesulfonyl)vinyl)-cyclohexane **28** (31 mg, 0.11 mmol, 68%) as a pale yellow oil. R_f (10% EtOAc/hex): 0.23. IR (NaCl plate): ν 1578, 1355 1207, 1120, 711. ^1H NMR (CDCl_3 , 400 MHz): δ 1.20-1.40 (m, 5H), 1.78-1.95 (m, 5H), 2.41-2.47 (m, 1H), 3.95 (s, 3H), 5.26 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 25.17, 25.55, 25.86, 31.28, 31.34, 39.79, 56.50, 93.85, 120.13 (q, $J = 326$ Hz), 183.56. ^{19}F NMR (CDCl_3 , 276 MHz): δ -78.33. HRMS (ESI-QTOF): m/z [$\text{M} + \text{H}^+$] calcd for $\text{C}_{10}\text{H}_{15}\text{F}_3\text{O}_3\text{S} + \text{H}$: 273.0772; found: 273.0739.



1-phenyl-2-(trifluoromethanesulfonyl)ethanone **10** (149 mg, 0.59 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure and the resulting material was purified by flash chromatography (45 g silica, 2 cm diameter column, 10% EtOAc/hex + 1% pyridine additive) to afford (Z)-(1-methoxy-2-(trifluoromethanesulfonyl)vinyl)benzene **30** (145 mg, 0.54 mmol, 92%) as a yellow oil. R_f (10% EtOAc/hex): 0.24. IR (NaCl plate): ν 1592, 1567, 1359, 1202, 1119, 700. ^1H NMR (CDCl_3 , 300 MHz): δ 3.83 (s, 3H), 5.64 (s, 1H), 7.45-7.63 (m, 5H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 60.53, 99.35, 120.10 (q, $J = 326$ Hz), 128.21, 129.28, 130.94, 132.34, 179.53. ^{19}F NMR (CDCl_3 , 282 MHz): δ -77.75. HRMS (ESI-QTOF): m/z [$\text{M} + \text{H}^+$] calcd for $\text{C}_{10}\text{H}_9\text{F}_3\text{O}_3\text{S} + \text{H}$: 267.0303; found: 267.0299.



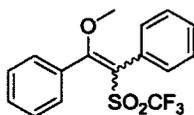
2-(trifluoromethanesulfonyl)pentan-3-one **14** (35 mg, 0.16 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure and the resulting material was purified by automated flash chromatography (10 g silica column, 0-5% EtOAc/hex) to afford (*Z*)-3-methoxy-2-(trifluoromethanesulfonyl)pen-2-ene (**Z**-**31**) (7 mg, 0.03 mmol, 20%) and (*E*)-3-methoxy-2-(trifluoromethanesulfonyl)pen-2-ene (**E**-**31**) (20 mg, 0.09 mmol, 57%) as yellow oils.

Trans (*E*)-**31**

R_f (10% EtOAc/hex): 0.35. IR (NaCl plate): ν 1600, 1349, 1194, 1118. ^1H NMR (CDCl_3 , 400 MHz): δ 1.24 (t, $J = 7.6$ Hz, 3H), 2.00 (s, 3H), 2.89 (q, $J = 7.5$ Hz, 2H), 3.94 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 12.40, 12.95, 20.95, 55.68, 104.82, 120.25 (q, $J = 327$ Hz), 177.70. ^{19}F NMR (CDCl_3 , 376 MHz): δ -77.98. HRMS: m/z calcd for $\text{C}_7\text{H}_{11}\text{O}_3\text{S}_1\text{F}_3$: 232.0381; found: 231.0384.

Cis (*Z*)-**31**

R_f (10% EtOAc/hex): 0.11. IR (NaCl plate): ν 1592, 1348, 1214, 1183, 1104. ^1H NMR (CDCl_3 , 400 MHz): δ 1.21 (t, $J = 7.2$ Hz, 3H), 2.05 (s, 3H), 2.50 (t, $J = 7.6$ Hz, 3H), 3.86 (s, 1H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 10.91, 13.04, 22.03, 56.36, 106.53, 120.33 (q, $J = 328$ Hz), 174.01. ^{19}F NMR (CDCl_3 , 376 MHz): δ -76.22. HRMS: m/z calcd for $\text{C}_7\text{H}_{11}\text{O}_3\text{S}_1\text{F}_3$: 232.0381; found: 231.0373.

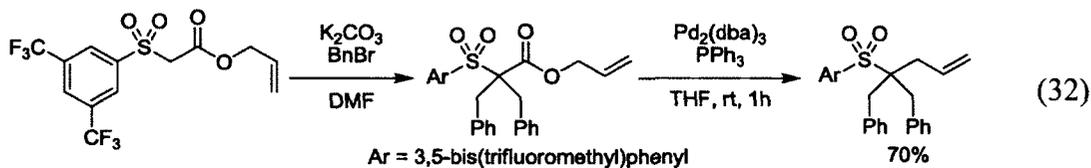
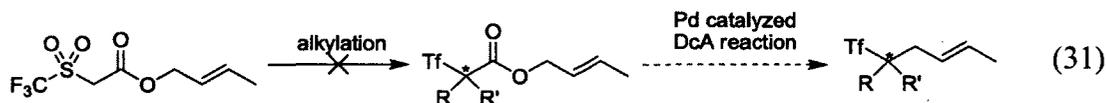


1,2-diphenyl-2-(trifluoromethanesulfonyl)ethanone **16** (44 mg, 0.13 mmol) was reacted with $\text{Me}_3\text{SiCHN}_2$ according to the general procedure and the resulting material was purified by automated flash chromatography (10 g silica column, 20% EtOAc/hex) to afford (1-methoxy-2-(trifluoromethanesulfonyl)ethane-1,2-diyl)dibenzene **32** (22 mg, 0.06 mmol, 48%) as a colorless oil. R_f (20% EtOAc/hex): 0.42. IR (NaCl plate): ν 1605, 1585, 1570, 1357, 1202, 1103, 771. ^1H NMR (CDCl_3 , 400 MHz): δ 3.36 (s, 3H, cis/trans), 3.72 (s, 3H, cis/trans), 7.19-7.76 (m, 10H, cis/trans). ^{13}C NMR (CDCl_3 , 100 MHz): δ 58.01, 59.63, 113.26, 117.41, 120.68 (q, $J = 327$ Hz), 129.20, 128.34, 128.38, 128.63, 128.70, 128.92, 129.51, 129.90, 130.05, 130.50, 130.58, 130.91, 131.92, 132.76, 172.40, 174.50. ^{19}F NMR (CDCl_3 , 376 MHz): δ -75.51, -74.82. HRMS (ESI-QTOF): m/z [$\text{M} + \text{Na}^+$] calcd for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{O}_3\text{S} + \text{Na}$: 365.0435; found: 365.0434.

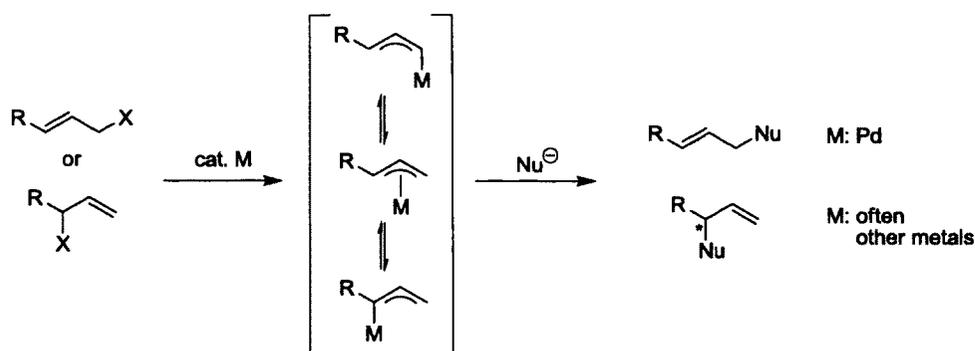
4 Chapter: Decarboxylative Allylation

As previously discussed, the alkylation of α -triflylcarbonyl compounds branched out from the preparation of substrates for the palladium catalyzed decarboxylative allylation (DcA) reaction, which is the on-going research program of our group.

Although the alkylation of α -triflyl carbonyl compounds resulted in interesting ambiphilic alkenes, the results did not solve the continued issue of alkylating these compounds. This research had been carried out by a colleague, Monica Gill, and had shown that an alternative electron withdrawing group, bis(trifluoromethyl)phenylsulfone, exhibited similar reactivity in the Pd-catalyzed DcA reaction, but the acidity of the α -position was marginally higher. This allowed the requisite alkylation to be easily performed (eq 32).⁴²



The decarboxylative allylation is developed from the Tsuji-Trost allylation reaction, which is well established and a number of transition metals have shown high reactivity and regio- and stereoselectivity. The regioselectivity was dependent on the transition metal. For example, when the allylic substitution was catalyzed by palladium, it resulted in the linear achiral products. However, in case of other metals such as iridium, it resulted in branched, chiral products (Scheme 15). Inspired by this iridium catalyzed DcA reaction, we chose to explore the decarboxylative allylation reaction on our substrates, allylic bis(trifluoromethyl)phenylsulfonyl acetate compounds.



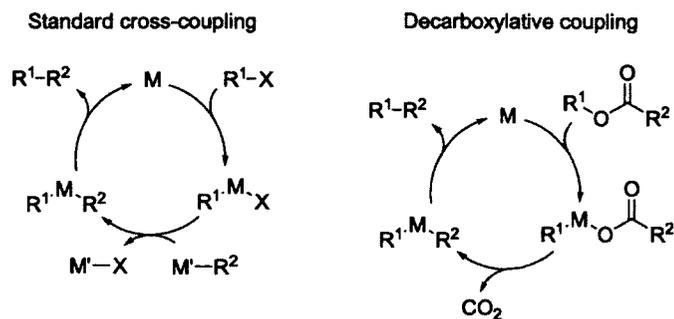
Scheme 15. General Regioselectivity of Transition Metal Catalyzed Allylation

4.1 Introduction to Decarboxylative Coupling Reactions

Cross-coupling reactions are the most powerful and versatile synthetic reactions to form a C-C bond formation between two different compounds using catalytic transition metals. Without a doubt, cross-coupling reactions have expanded the scope of organic synthesis of simple and complex molecules for pharmaceuticals and natural products. Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki, who had developed palladium catalyzed cross coupling reactions, were awarded the Nobel Prize in Chemistry 2010.⁴³

Although there are a number of cross-coupling reactions depending on the transition metal, the general mechanism typically involves the oxidative addition of an aryl or alkyl halide to a transition metal, followed by the transmetalation and the reductive elimination of the desired coupled products. These reactions have been developed to afford the products in chemo-, regio-, and stereoselective fashion. There are, however, a few drawbacks, such as the need of the preparation of adequate organometallic compounds ($M'-R^2$, Scheme 16). Also it results in a stoichiometric amount of hazardous metal salt waste ($M'-X$) that can complicate the purification of products.

Given these downsides of cross-coupling reactions, alternative strategies for the generation of organometallic intermediates are highly desirable along with inexpensive substrates, mild conditions, and easily removable wastes.

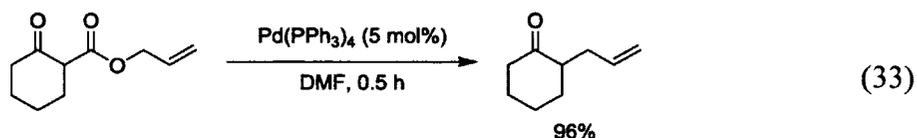


Scheme 16. Standard Cross-Coupling and Decarboxylative Coupling

The decarboxylative allylation reaction is a specific type of coupling reaction where the catalytic metal binds to the substrate, and the subsequent decarboxylation generates an organometallic intermediate. This then undergoes the reductive elimination to afford the coupled product. As compared to traditional cross-coupling reactions, the decarboxylative coupling reactions have several potential advantages. First of all, the substrates are carboxylic acid derivatives that are inexpensive and easily made. Secondly, the formation of the reactive organometallic intermediate is driven by the decarboxylation under mild and neutral conditions. Moreover, the only stoichiometric byproduct is the CO_2 , which is nonflammable, non-toxic, and easily removed from the reaction system.

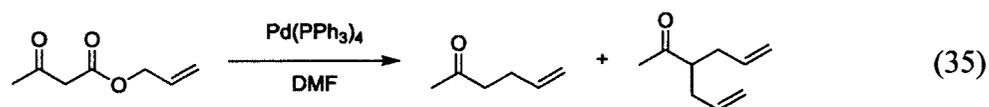
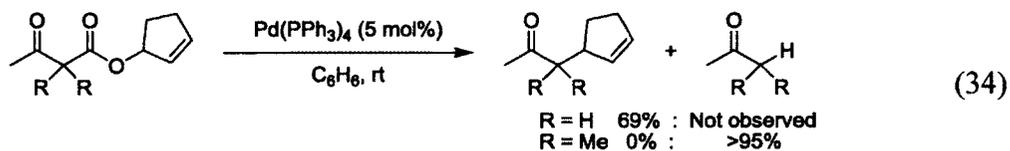
4.1.1 Decarboxylative Allylation Reaction

In typical Tsuji-Trost reaction,⁴⁴ an allylic acetate or carbonate was reacted with a palladium catalyst to generate via π -allylpalladium complexes that can undergo nucleophilic substitution. The first decarboxylative allylation (DcA) reaction was reported by Tsuji⁴⁵ and Saegusa⁴⁶ independently in 1980 with β -keto allyl esters (eq 33). In this reaction, the loss of CO₂ replaced the need of strong base for nucleophiles, thus making the reaction medium fairly neutral. Both the nucleophile and π -allylpalladium complexes were generated *in situ*.

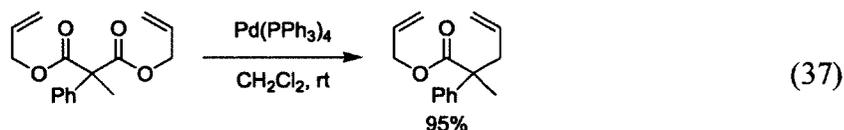
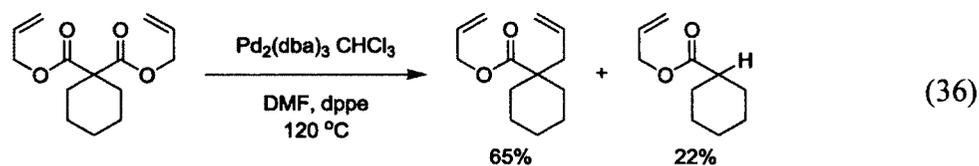


After the first disclosure of DcA reaction from Tsuji and Saegusa, it has been developed and studied intensively. Even though the scope of the reaction is well-studied, the mechanism is still not well defined.⁴⁷ The reaction was successfully extended to intermolecular allylation,⁴⁸ and asymmetric methods are known.^{49,50,51}

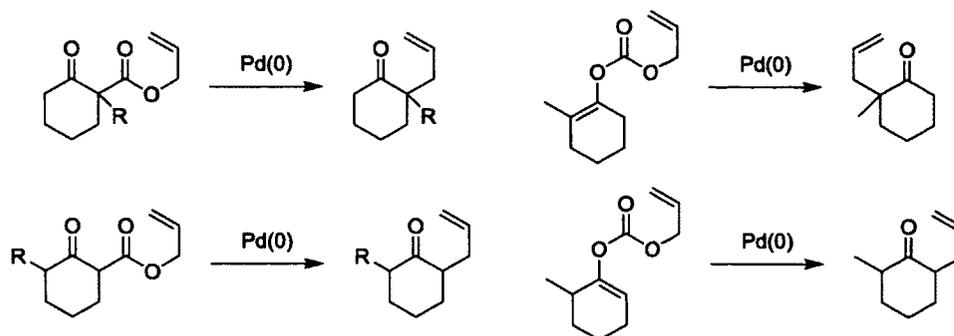
In the DcA reaction, there are two common byproducts; protonation of the enolate and diallylation. The protonation is prone to occur frequently when α -position of β -ketoester is substituted (eq 34).⁵² The diallylation is thought to be a result from a combination of DcA reaction and Tsuji-Trost allylation of the ketoester (eq 35).



Tsuji and co-workers showed the protonated byproduct from DcA reaction of malonate derivatives (eq 36).⁵³ This reaction was very slow and required high temperature (120 °C). In a recent paper from Ohta, the DcA reaction of α -aryl malonic derivatives was took place easily at room temperature (eq 37).⁵⁴ This illustrated the dependency of DcA reaction rate on the stability of incipient enolate. In other words, the facile formation of enolate allows the faster and easier decarboxylation.

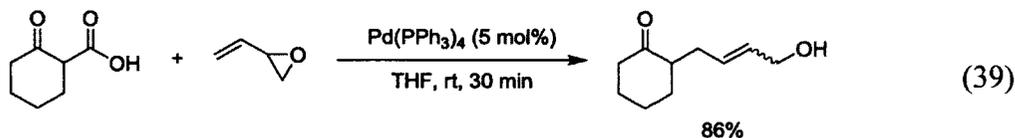
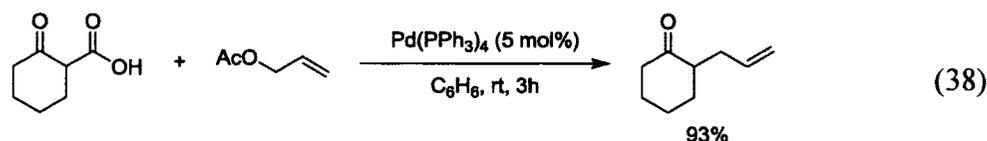


The regioselectivity of the DcA reaction is a significant advantage in comparison to traditional allylation reactions, because the decarboxylation allowed the site-specific formation of an enolate where it bears CO₂ (Scheme 17).⁵⁵ The enolate from decarboxylation does not isomerize into the thermodynamically more stable enolate; instead, it rapidly reacts with allyl electrophiles to give the product. This regiospecific formation of enolate would be difficult to achieve in the traditional allylation by acid-base chemistry. Another example of the regioselectivity of DcA reaction was the allylation of allyl vinyl carbonates, which still required a traditional base-induced enolization to prepare.

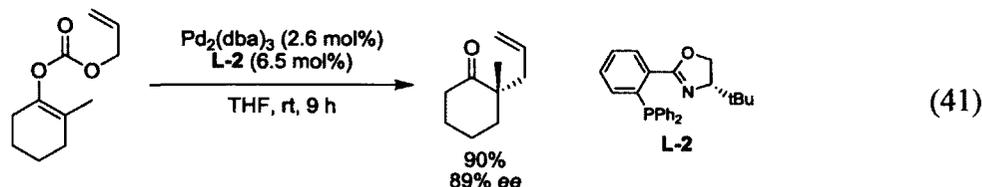
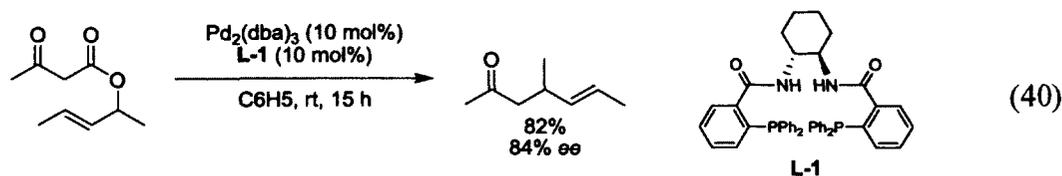


Scheme 17. Regioselectivity of DcA Reaction

Since those aforementioned DcA reactions are intermolecular coupling reactions, one possible drawback could be the preparation of appropriate substrates of allyl β -ketoester that was made from corresponding acid and allyl alcohol. To avoid the preparation of the esters, Saegusa and co-workers has shown the intermolecular DcA reactions of β -ketocarboxylic acid with allyl acetate or vinyl epoxides (eq 38 and 39).⁴⁰



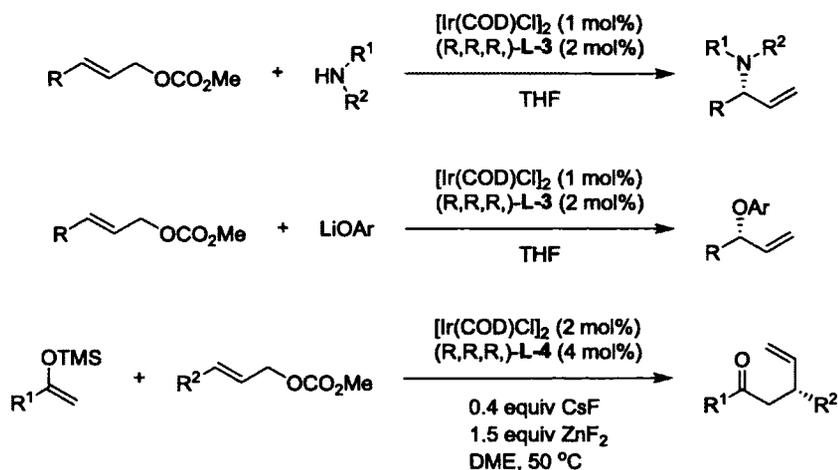
The further study of DcA reaction has led to the control of stereochemistry at various positions using chiral ligands. While Tunge and co-workers showed the enantioselective DcA reaction at β -carbon of allylic β -ketoester using Trost ligand **L-1** (eq 40),⁴⁹ Stoltz⁵⁰ and Trost⁵¹ demonstrated the enantioselectivity at α -carbon from vinyl allylic carbonate (eq 41). On top of those two examples, there are many other methodologies to control the stereochemistry of DcA reaction; however, an extensive discussion of these methods is beyond the scope of this thesis.



4.1.2 Iridium Catalyzed Decarboxylative Allylation

Different reactivity and selectivity can be observed when the same substrate is treated with different transition metals. Tsuji-Trost allylation reaction have been developed with other transition metals, such as copper,⁵⁶ molybdenum,⁵⁷ tungsten,⁵⁸ rhodium,⁵⁹ and iridium.^{60,61} Among these metals, palladium catalysis is unique in that it typically yields linear, achiral products, while other metals afford branched, chiral products (Scheme 15).

Among those transition metals, iridium has been studied thoroughly by Helmchen⁶⁰ and Hartwig⁶¹ from the late 1990s through to the present. Their independent work has led them to similar conclusions. Through intensive study, it has been well established that iridium catalyzes the decarboxylative allylation reaction to couple allyl moieties with not only carbon nucleophiles^{62,63,64,65} but also nitrogen^{66,67} and oxygen nucleophiles^{68,69,70} in a highly regioselective fashion, affording the branched products (Scheme 18). For the highest enantioselectivity, phosphoramidite ligands (Figure 4) were found to be the most effective.



Scheme 18. General DcA Reaction Schemes with C-, N-, and O-nucleophiles

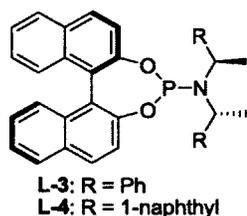
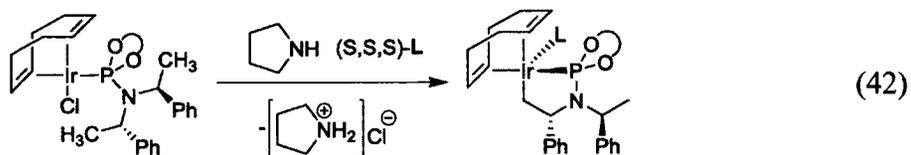


Figure 4. Structure of Phosphoramidite Ligands

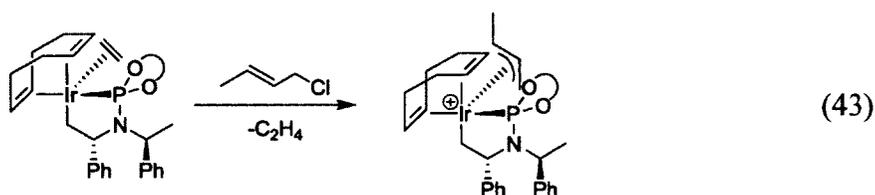
A study of the active catalytic species had found an interesting metallacycle species which definitely participates in the catalytic cycle. This had led a better understanding of the mechanism. As the phosphoramidite ligand was coordinated to the iridium center, it underwent an intramolecular C-H activation of the ligand methyl group to form the five-coordinate metallacycle containing one cyclometalated κ^2 -phosphoramidite and one κ^1 -phosphoramidite (eq 42).^{67c}



This intermediate was prepared and isolated separately for DcA reaction by mixing $[\text{Ir}(\text{COD})\text{Cl}]_2$ with the phosphoramidite ligand in the presence of a weak base, such as propylamine. Also, a more stable analogue was formed when κ^1 -phosphoramidite was replaced with ethylene. This ethylene-iridium intermediate (eq 43) could be prepared on a multigram scale in a single step and still can be used readily for DcA reaction.

Hartwig conducted tests to show that the metallacycle intermediate, prepared *in situ* or generated separately and isolated, participates in the catalytic cycle. The result was the reactions with preactivated catalyst occurred faster than reaction with the original system.

67c



Moreover, when the ethylene of the ethylene-iridium intermediate was replaced with a crotyl moiety, the resulting crotyliridium species allowed the growth of crystals suitable for X-ray diffraction (eq 43).⁷¹ This crystallograph proposed the activated catalyst was the metallacycle species. From this, the high enantioselectivity of the Ir-phosphoramidite could be explained. The cyclooctadiene ligand and BINOLate substituent on phosphorus restrict the binding site of allyl ligand, so that the substituted termini of the allyl ligand are located on the exterior of the complex, and, therefore, more susceptible to nucleophilic attack.

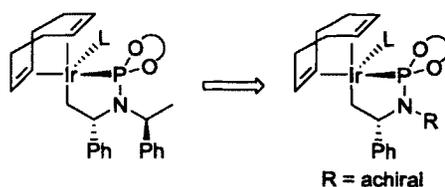
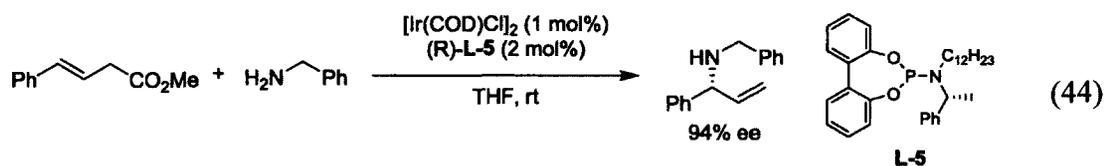


Figure 5. Elimination of One Stereochemical Element in the Active Catalyst

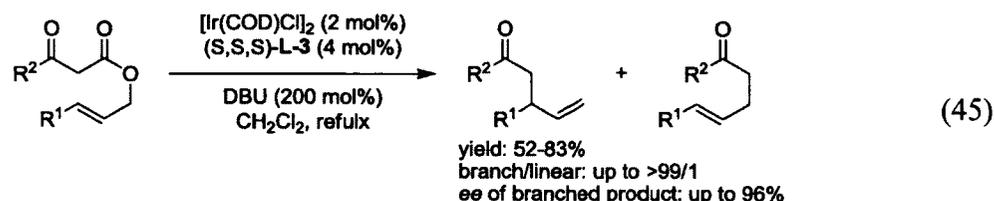
Phosphoramidite ligands are highly versatile and numerous variations can be easily made. Based on the structure of active metallacycle catalyst, it appeared that the distal phenethyl substituent on the nitrogen from the metal core did not participate in controlling enantioselectivity of products, so that it could be replaced with other achiral substituents (Figure 5). It was replaced with a bulky cyclic hydrocarbon group, such as cyclododecyl moiety, and it still resulted in the high enantioselectivity in the DcA reaction.⁷² In order to determine whether the binaphtholate substituent on phosphorus was controlling the enantioselectivity or the remaining phenethyl on nitrogen, a ligand containing biphenolate, instead of binaphtholate, was prepared with phenethyl and dodecyl groups on nitrogen. This ligand (**L-5**) had only one stereochemical element, and it had still resulted in the enantioselectivity as high as the reaction with original phosphoramidite ligand **L-3** (eq 44).



4.1.3 Decarboxylative Research Goal

The decarboxylative allylation is a modification of Tsuji-Trost allylation where the generation of the nucleophile is induced by decarboxylation *in situ*, which

simultaneously results in the formation of a π -allyl iridium complex. Since iridium also can catalyze the Tsuji-Trost allylation, You and co-workers have reported the iridium catalyzed DcA reaction on γ -substituted allyl β -keto carboxylate affording high regio- and enantioselectivity.⁷³



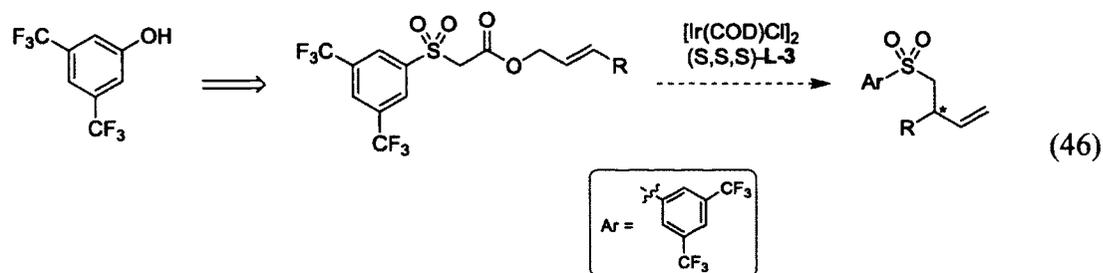
In order for DcA reaction to take place, the formation of a stable nucleophile from the decarboxylation is essential. It leads to a limitation that the substrates must be allylic β -keto esters, so that the β -keto group contributes the facile formation of the enolate and decarboxylation. Thus, it was proposed that an α -sulfonyl group, instead of β -keto, could facilitate the DcA reaction since the sulfonyl group is also a strong electron-withdrawing group and it stabilizes the negative charge on adjacent carbon as the keto group. My colleague, Monica Gill, has shown the DcA reaction of dialkylated bis(trifluoromethyl)phenylsulfonyl esters catalyzed by the palladium under mild conditions (eq 32). Based on the precedence in the literature for the decarboxylative allylation reaction catalyzed by iridium, we chose to explore this chemistry on α -unsubstituted substrates.

4.2 Iridium Catalyzed Decarboxylative Allylation

4.2.1 Experimental Approach

The preparation of allylic bis(trifluoromethyl)phenylsulfonyl acetate from 3,5-bis(trifluoromethyl)phenol was already well established by a colleague, Monica Gill. For

the DcA reaction, the activated catalyst would be prepared *in situ* using $[\text{Ir}(\text{COD})\text{Cl}]_2$ and phosphoramidite **L-3** prior to addition of the α -sulfonyl ester.

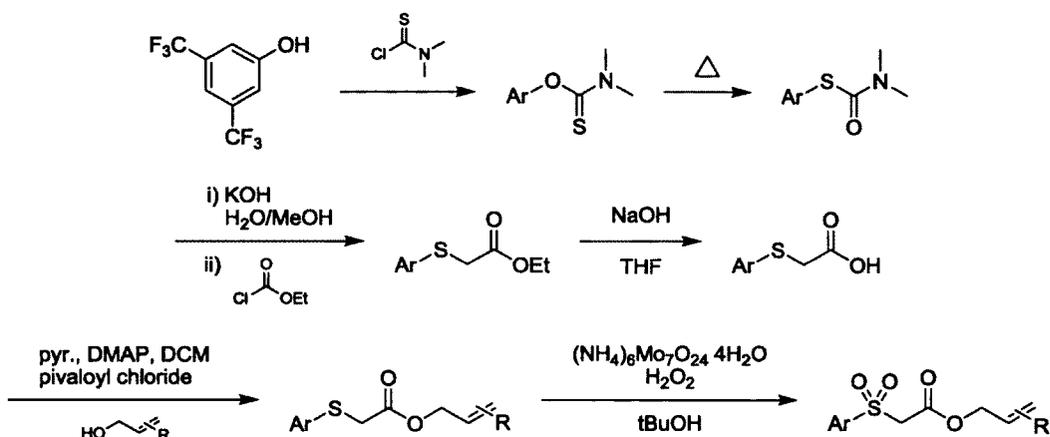


In order to validate the iridium catalyzed DcA reaction, it was essential to analyze the regioselectivity and enantioselectivity. As a chiral ligand was used in reactions, it was expected to afford an enantioenriched product. Once the DcA reaction successfully affords the desired γ,δ -unsaturated sulfone, the enantioselectivity would be determined by GC by using a chiral stationary phase. The regioselectivity can be readily analyzed by NMR spectral data.

4.2.2 Preparation of Substrates

The preparation of various allylic α -bis(trifluoromethyl)phenylsulfonyl acetates is illustrated in Scheme 19. 3,5-Bis(trifluoromethyl)phenol was subjected to an acylation reaction with dimethylthiocarbamoyl chloride, affording the O-thiocarbamate. This was thermally rearranged to the S-thiocarbamate. It was then hydrolyzed under basic conditions to give the substituted thiophenolate, which was alkylated *in situ* with ethyl chloroacetate to afford the α -thio acetate, which was hydrolyzed to the corresponding carboxylic acid. The acid was reacted with pivaloyl chloride, forming the mixed anhydride intermediate, followed by a reaction with various allylic alcohols to give corresponding allylic α -thioacetates.⁷⁴ Then, the thioether was selectively oxidized into

the sulfonyl group using hydrogen peroxide and catalytic ammonium molybdate to afford the allylic α -bis(trifluoromethyl)-phenylsulfonyl acetates.

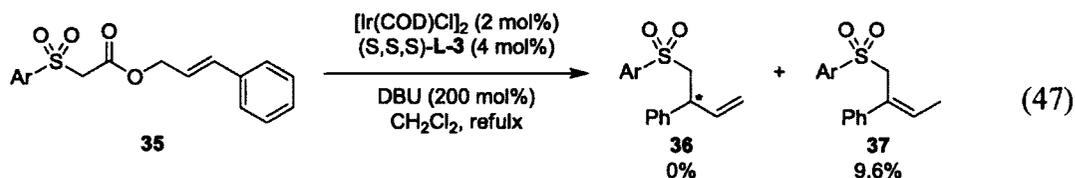


Scheme 19. Preparation of Allylic α -bis(trifluoromethyl)phenylsulfonyl Acetates

4.2.3 Iridium Catalyzed Decarboxylative Allylation

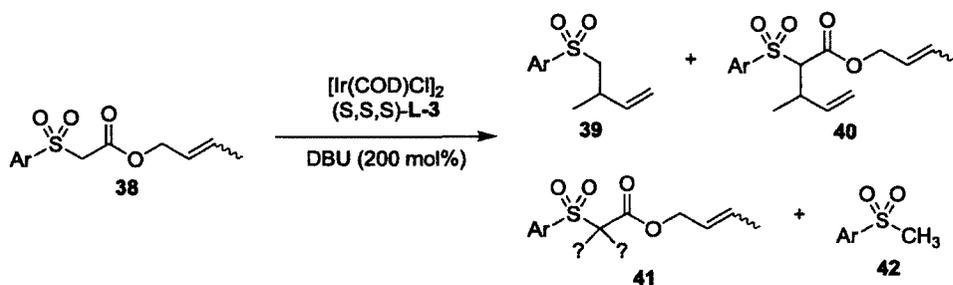
With the established preparation procedure for various substrates, cinnamyl α -(3,5-bis(trifluoromethyl)phenylsulfonyl)acetate **35** was selected for the first attempt of the iridium catalyzed decarboxylative allylation reaction with phosphoramidite L-3.

Based on the You's procedure,⁷³ the active catalyst was prepared *in situ* using propylamine and used immediately. Even though it had exhibited the expected regioselectivity to form the branched product, this reaction was unsuccessful in terms of yield and the migration of the double bond (eq 47).



The expected product was the compound **36**, in which the alkene double bond would be located at the terminal carbon. However, the only recognizable product from the reaction was compound **37**, where it was appeared that the double bond had migrated into conjugation with the aromatic ring. To support this finding, methylene hydrogens on the α -carbon and methyl hydrogens on δ -carbon were observed as clear doublets (Appendix C.1.1). Thus, no chiral center was obtained. Such a migration of the double bond in cinnamyl system was not unprecedented.⁷⁵ Importantly, this experiment had shown that iridium could catalyze the DcA reaction on allylic α -(3,5-bis(trifluoromethyl)phenylsulfonyl)acetate and regioselectively afford the branched products.

Table 9. Optimization of DcA Reaction with α -Sulfonyl Ester **38**^a



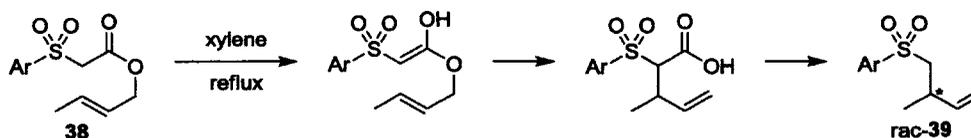
Entry	[Ir(COD)Cl] ₂	Solvent	Conc.	Temp.	Product
1	2 mol %	DCM	0.1 M	Reflux	39 (18.6%) 40 (1.5%)
2	2 mol %	DCM	0.01 M	Reflux	41
3	2 mol %	DCM	0.5 M	Reflux	40 (2%) 41
4	5 mol %	DCM	0.1 M	Reflux	39 (30%) 42 (64%)
5	5 mol %	THF	0.1 M	Reflux	39 (51%) 42 (43%)
6	5 mol %	Toluene	0.1 M	75 °C	39 (42%) 42 (43%)
7	5 mol %	Ether	0.1 M	Reflux	39 (16%) 42 (42%)

^a 0.25 mmol of **38** was used for all entries, and amount of L-**3** was twice of [Ir(COD)Cl]₂ for all entries.

To optimize the Ir-catalyzed DcA reaction, the substrate was switched to crotyl α -(3,5-bis(trifluoromethyl)phenylsulfonyl)acetate **38**, which does not have the phenyl group to conjugate to in the expected product. The results were summarized in Table 9. Under the original conditions, the DcA reaction on α -triflyl ester **38** had resulted in the formation of the expected branched product **39**, and no linear product was observed. A small amount of sulfone **40** was also observed, and it seemed to be the result of the intermolecular allylation on itself, where the α -triflyl ester **38** acted as both nucleophiles and allyl moiety source (entry 1). The formation of sulfone **40** could be avoided if the concentration of the reaction was decreased. The reaction conducted in a lower concentration resulted in the undetermined byproduct **41**, that it seemed to still resemble the allyl α -triflyl ester in the ¹H NMR spectrum; but, the α -methine hydrogen was absent (entries 2 and 3). Another method of reducing the intermolecular reaction was the addition of more catalyst to increase the rate of decarboxylation to consume α -triflyl ester **38** before it acts as a nucleophile.

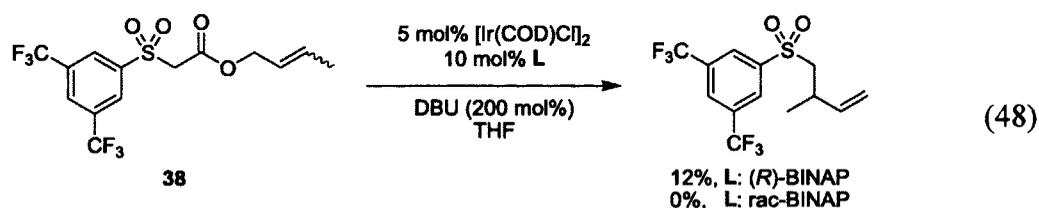
When the amount of the iridium and ligand were increased to 5 mol% or 10 mol%, the reaction yielded not only more DcA product sulfone **39** but also sulfone **42**, which was a common byproduct of the DcA reaction (entry 4). A solvent screen was performed using THF, toluene, and ether (entries 5,6, and 7). The byproduct sulfone **42** was still observed from all solvents, but less than with DCM, and THF showed the most conversion and isolation of product sulfone **39** and byproduct sulfone **42** (entry 5).

The results from Table 9 supported that the iridium catalyzed DcA reaction on our substrates proceeds in the typical regioselective manner toward the branched products. Before we further optimized the reaction to increase the yield of product and avoid the formation of byproduct **42**, it was essential to analyze the enantiomeric excess (*ee*) of product **39**.



Scheme 20. Carroll Rearrangement on Compound **38**

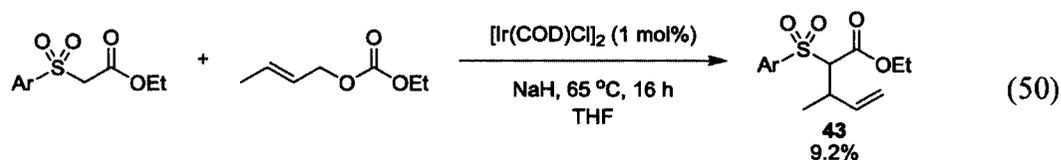
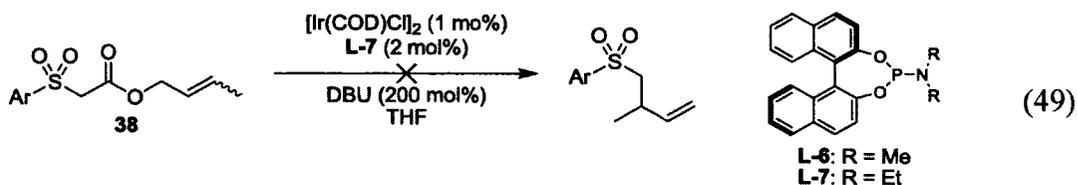
A racemic mixture of the sulfone **39** was required to analyze the *ee* of the product. The first approach was by the Carroll rearrangement, which is a combination of [3,3]-sigmatropic rearrangement and the decarboxylation by the Claisen rearrangement (Scheme 20)^{8b,76} In overall, the product of the Carroll rearrangement on an allylic β -ketoesters is γ,δ -unsaturated ketone, which is same as the product from the DcA reaction. However, the Carroll rearrangement on α -triflyl ester **38** was futile as there was no change in ¹H NMR spectrum.



Another approach to the racemic mixture of sulfone **39** was the direct DcA reaction with an achiral or racemic ligand. The first attempt was using rac-BINAP as the ligand, and no reaction was observed. It succeeded, however, in 12% yield when (*R*)-

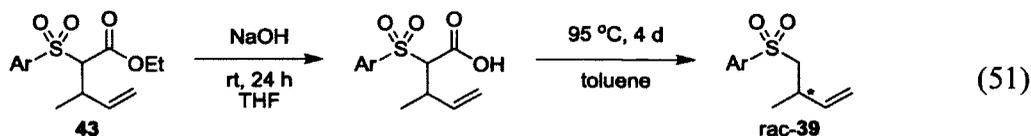
BINAP was used, and the reaction did not occur with *rac*-BINAP (eq 48). It was theorized that when two different enantiomers of *rac*-BINAP were attached to iridium, the catalyst lost its reactivity.

In 1999, Helmchen had developed an intermolecular Ir-catalyzed allylation between allylic carbonate and malonate with a ligand, phosphoramidite **L-6**.^{66a} As it was introduced in section 3.1.2, the stereocenter on the nitrogen substituent, which made the core metallacycle, was more responsible for controlling the enantioselectivity of products.⁷² Thus, it was postulated that the use of ligand with achiral substituents on nitrogen would result in a poor enantioselectivity through the DcA reaction. Unfortunately, the direct formation of the racemic mixture of the product from α -triflyl ester **38** using ligand **L-7** was unsuccessful, resulting in the decomposition of compound **38** (eq 49).

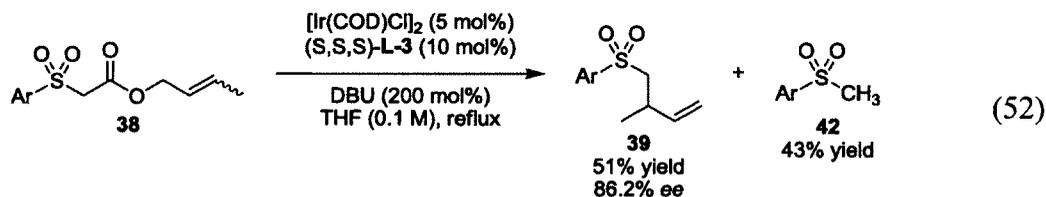


Then, it was attempted to follow Helmchen's intermolecular Ir-catalyzed allylation with ethyl bis(trifluoromethyl)phenylsulfonate on ethylcrotyl carbonate using **L-7** (eq 50). The yield was poor; nevertheless it afforded the desired compounds. Moreover, the reaction afforded the diastereoisomeric mixture of sulfonamide ester **43** without any additional ligands. Sulfonamide ester **43** was hydrolyzed and a thermally induced

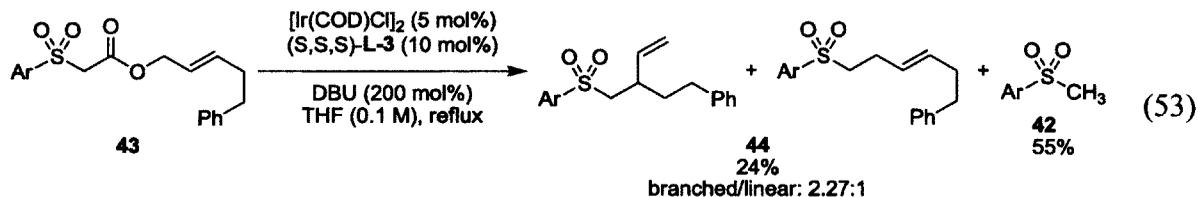
decarboxylation under a basic condition afforded the racemic mixture of sulfone **39** (eq 51).



With the racemic mixture of sulfone **39** in hand, compounds were analyzed by the GC equipped with a chiral column to separate the enantiomers. The isomers were eluted at 16.432 and 17.472 minutes. The later isomer was the major product from Ir-catalyzed DcA reaction with **L-3** with a ratio of 10.7:1, which corresponded to an *ee* of 86.2%.



Another allyl sulfonylacetate compound **43** was subjected to the DcA reaction under the same conditions of 5 mol% of iridium in THF (eq 53). Unfortunately, it resulted in the low regioselectivity as the mixture of branched and linear product **44** was obtained, yet, in the ratio of 2.27:1 with the typical protonated byproduct **42**.



Thus, these results demonstrated that the Ir-catalyzed DcA reaction with **L-3** on allylic α -sulfonyl esters I substrate dependent but can be highly regio- and enantioselective. Though the yield was poor and a significant byproduct was formed, the reaction has not yet been fully optimized.

4.2.4 Future Work & Conclusion

To conclude, it was shown that the iridium catalyzed decarboxylative allylation reaction on allylic α -bis(trifluoromethyl)phenylsulfonyl acetates was feasible. The first attempt on α -sulfonyl ester **35** with phosphoramidite ligand **L-3** resulted in particularly low yield. It also showed the reaction afforded branched products, but the phenyl group induced migration of the double bond into the conjugation yielding sulfone **37**. The reaction was then optimized on α -sulfonyl ester **38** to afford the branched product **39** in good regioselectivity and enantioselectivity (86.2% *ee*). The yield was moderate at 50% and a significant amount of the protonated byproduct **42** was formed. Another substrate **43** was tested, but the result was a mixture of branched and linear product **44**. It still favored the branched product over linear with the ratio of 2.72:1. The origin of the proton on the byproduct remains still unclear. Yet, the DcA reaction has not been fully optimized. Higher boiling solvents, such as 1,4-dioxane, providing the higher reaction temperature, remain to be screened. Also, we could apply further additives and alternative bases to propylamine that can be screened for increase in yields and suppression of the protonated byproduct.

5 Chapter: Experimental Procedure for Decarboxylative Allylation

5.1 General Experimental

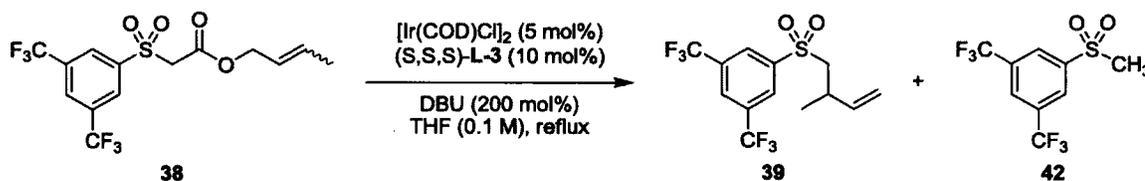
All reagents were purchased from commercial sources such as Sigma-Aldrich, Strem, and TCI, and were used as received without further purification. All non-aqueous reactions were carried out under a positive pressure of dry nitrogen or argon atmosphere. THF was distilled from CaH₂ prior to use. Except as indicated otherwise, reactions were magnetically stirred and monitored by TLC using glass-backed Extra Hard Layer (60 Å) TLC plates from Silicycle and visualized by fluorescence quenching under UV light and/or staining using potassium permanganate. Flash chromatographic purification of products was performed either on Silia-P Flash silica gel from Silicycle using a forced flow of eluent by the method of Still³⁴ or by automated chromatography on a Biotage Isolera One equipped with a UV detector. Concentration *in vacuo* refers to rotary evaporation at 40 °C under the appropriate pressure. Yields refer to purified and spectroscopically pure compounds unless explicitly indicated as crude.

NMR spectra were recorded on Bruker Avance III 300 or Bruker AMX 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as internal standard for ¹H and ¹³C NMR spectra. ¹⁹F NMR spectra are referenced to α,α,α-trifluorotoluene (-63.7 ppm). IR spectra were recorded on a Varian 1000 Scimitar Series. Absorptions are given in wavenumbers (cm⁻¹). High-resolution mass spectrometry was conducted using an ABI Sciex QSTAR XL electrospray quadrupole-time-of-flight (ESI-QTOF) spectrometer with cesium iodide as an internal reference, or on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV at the Ottawa-Carleton Mass Spectrometry Center. Enantiomeric ratios were determined using gas chromatographic

analysis with a chiral column (Varian CP Chirasil-Dex CB WCOTFused Silica, 25 m x 0.25 mm). The samples were dissolved in methanol and an injection volume of 1.0 μL was used. The injector was held at 250 $^{\circ}\text{C}$, and the initial column oven temperature was 120 $^{\circ}\text{C}$. The column oven temperature was held at 120 $^{\circ}\text{C}$ for 20 minutes following injection, then was ramped to 190 $^{\circ}\text{C}$ at a rate of 20 $^{\circ}\text{C}/\text{minute}$, followed by a 10 minute hold period at 190 $^{\circ}\text{C}$. The ratios were determined via comparison of peak area on the chromatogram.

5.2 Iridium-Catalyzed Decarboxylative Allylation

General Procedure for the Iridium-catalyzed Decarboxylative Allylation (Entry 5, Table 8)



A flame dried Schlenk flask was cooled to room temperature and charged with argon/nitrogen. To this flask were added $[\text{Ir}(\text{COD})\text{Cl}]_2$ (8.5 mg, 0.012 mmol, 5 mol%), phosphoramidite ligand L-3 [(S)-(+)-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']dinaphthalen-4-yl)bis[(1S)-1-phenylethyl]amine] (13.7 mg, 0.025 mmol, 10 mol%), THF (1.59 mL), and propylamine (1.59 mL). The reaction mixture was heated at 60 $^{\circ}\text{C}$ for 30 min. Then the solvent was removed *in vacuo*. After that, but-2-enyl 2-(3,5-bis(trifluoromethyl)phenylsulfonyl)acetate **38** (99.0 mmg, 0.25 mmol, 1 equiv.), DBU (0.76 mL, 51 mmol, 2 equiv.), and THF (2.54 mL) was added. The mixture was refluxed for overnight. Once the reaction was complete (the disappearance of **38**, monitored by TLC), the reaction mixture was concentrated under reduced pressure and the residue was

purified by flash chromatography (20 g silica, 2 cm diameter column, 5% EtOAc/Hex) to afford 1-((2-methylbut-3-en-1-yl)sulfonyl)-3,4-bis(trifluoromethyl)benzene **39** (45.1 mg, 130 μ mol, 51%) as pale yellow oil. Then the column was flush with EtOAc to obtain 1-(methylsulfonyl)-3,4-bis(trifluoromethyl)benzene **42** (31.8 mg, 109 μ mol, 43%) as brown solid.

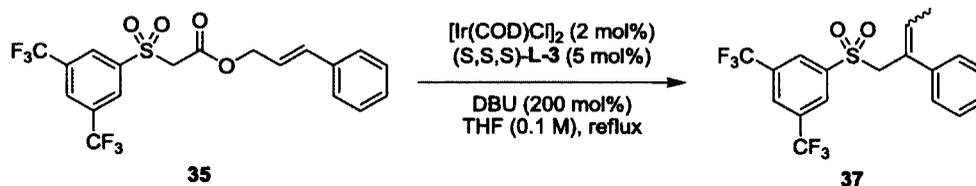
1-((2-methylbut-3-en-1-yl)sulfonyl)-3,4-bis(trifluoromethyl)benzene **39**

R_f (5% EtOAc/Hex): 0.27, R_f (20% EtOAc/Hex): 0.58. IR (NaCl plate) ν 2935, 2869, 1674, 1360, 1280, 1184, 1146, 1107, 772. ^1H NMR (CDCl_3 , 400 MHz): δ 1.24 (d, $J = 6.8$ Hz, 3H), 2.90 (septet, $J = 6.8$ Hz, 1H), 3.16 (dd, $J_1 = 6.2$ Hz, $J_2 = 14.2$ Hz, 1H), 3.25 (dd, $J_1 = 7.2$ Hz, $J_2 = 14.4$ Hz, 1H), 5.01 (d, $J_{cis} = 10.4$ Hz, 1H), 5.06 (d, $J_{trans} = 17.2$ Hz, 1H), 5.65 (ddd, $J_1 = 7.4$ Hz, $J_{cis} = 10$ Hz, $J_{trans} = 17.2$ Hz, 1H), 8.17 (s, 1H), 8.39 (s, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 20.48, 33.15, 62.01, 115.63, 122.35 (q, $J = 271.6$ Hz), 127.31 (t, $J = 3.5$ Hz), 128.66 (d, $J = 4$ Hz), 133.2 (q, $J = 36.7$ Hz), 139.89, 142.84. ^{19}F NMR (CDCl_3 , 376 MHz): δ -63.90. HRMS: m/z calcd for fragment $\text{C}_8\text{H}_5\text{F}_6\text{O}_2\text{S}$: 278.9914; found: 297.9916; calcd for fragment C_5H_8 : 68.0626; found: 68.0627. GC/FID: retention time: 16.432 minute for minor isomer and 17.472 minute for major isomer.

1-(Methylsulfonyl)-3,4-bis(trifluoromethyl)benzene **42**

R_f (5% EtOAc/Hex): 0, R_f (20% EtOAc/Hex): 0.13. IR (NaCl plate) ν 3093, 2931, 1625, 1301, 1278, 1135, 770. ^1H NMR (CDCl_3 , 400 MHz): δ 3.18 (s, 3H), 8.19 (s, 1H), 8.44 (s, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 44.40, 122.30 (q, $J = 271.67$ Hz), 127.49 (p, $J = 3.5$

Hz), 128.01 (d, $J = 3$ Hz), 133.45 (q, $J = 34.3$ Hz), 143.21. ^{19}F NMR (CDCl_3 , 376 MHz): δ -63.89. HRMS: m/z calcd for $\text{C}_9\text{H}_6\text{F}_6\text{O}_2\text{S}$: 291.9993; found: 291.9978.



Prepared according the general procedure using cinnamyl 2-(3,5-bis(trifluoromethyl)phenylsulfonyl)acetate (90.0 mg, 0.292 mmol, 1 equiv.) with $[\text{Ir}(\text{COD})\text{Cl}]_2$ (2 mol%) and L-3 (5 mol%) to afford 1-((2-Phenylbut-2-en-1-yl)sulfonyl)-3,3-bis(trifluoromethyl)benzene **37** (11.4 mg, 0.028 mmol, 9.6%) as white solid.

R_f (10% EtOAc/hex): 0.31. IR (NaCl plate) ν 3082, 2930, 1307, 1276, 1140, 751. ^1H NMR (CDCl_3 , 400 MHz): δ 1.92 (d, $J = 6.8$ Hz, 3H), 4.51 (s, 2H), 6.18 (t, $J = 7.1$ Hz, 1H), 6.96 (m, 2H), 7.10 (m, 3H), 7.88 (s, 1H), 8.09 (s, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 15.28, 57.14, 122.21 (q, $J = 271.6$ Hz), 125.95, 126.98 (t, $J = 2.0$ Hz), 127.49, 128.07, 128.53, 129.00 (d, $J = 3.0$ Hz), 132.52 (q, $J = 34.3$ Hz), 134.18, 139.79, 141.53. ^{19}F NMR (CDCl_3 , 376 MHz): δ -64.00.

References

1. For support for this theory, see (a) Wolfe, S.; Fernando, L. L. *Tetrahedron Lett.* **1983**, *24*, 3789–3792; (b) Wolfe, S.; Stolow, A. *Tetrahedron Lett.* **1983**, *24*, 4071–4074.
2. For the use of sulfone in total synthesis: (a) Smith, A. B., III, Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685-1688; (b) Smith, A. B., III, Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685-1688; (c) Boeckman, R. K., Jr., Yoon, S. K., Heckendorn, D. K. *J. Am. Chem. Soc.* **1991**, *113*, 9682-9684; (d) Rigby, J. H., Warshakoon, N. C., Payen, A. *J. Am. Chem. Soc.* **1999**, *121*, 8237-8245.
3. (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon: New York, 1993; (b) Durst, T. Sulphones. in *Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds Vol.3*; Jones, N. D., Eds.; Pergamon: New York, 1979; pp 171-196; (3) El-Awa, A.; Noshi, M. N.; Jourdin, du, X. M.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315–2349.
4. (a) Field, L. *J. Am. Chem. Soc.* **1952**, *74*, 3919–3921; (b) McFarland, J.; Buchanan, D. N. *J. Org. Chem.* **1965**, *30*, 2003–2007; (c) Truce, W. E.; Klingler, T. C. *J. Org. Chem.* **1970**, *35*, 1834–1838.
5. (a) Campbell, R. V. M.; Crombie, L.; Findley, D. A. R.; King, R. W.; Pattenden, G.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 897-913; (b) Kraus, G.; Frazier, K. *Synth. Commun.* **1978**, *8*, 483-486; (c) Hirama, M. *Tetrahedron Lett.* **1981**, *22*, 1905–1908; (d) Adams, J.; Bowler, J.; Collins, M.; Jones, D.; Swallow, S. *Tetrahedron Lett.* **1990**, *31*, 4355–4358.

6. (a) Happer, D. A. R.; Steenson, B. F. *Synthesis* **1980**, 806–807; (b) Tanikaga, R.; Tamura, T.; Nozaki, Y.; Kaji, A. *J. Chem. Soc., Chem. Commun.* **1984**, 87–88; (c) Dressler, H.; Graham, J. E. *J. Org. Chem.* **1967**, *32*, 987–990.
7. Caubere, P.; Courtro, P. Reduction of Sulfur-Carbon Bonds and of Other Heteroatoms Bonded to Tetrahedral Carbon. In *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry* [Online]; Trost, B. M.; Fleming, I.; Elsevier: New York, 1991; Volume 8, Chapter 4.3, pp 835–847.
http://www.knovel.com/web/portal/browse/display?_EXT_KNOVEL_DISPLAY_bookid=1726&VerticalID=0 (accessed November 24, 2011).
8. (a) J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Bull. Soc. Chim. Fr.* 1993, *130*, 336–357; (b) Kürti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: New York, 2005.
9. Bordwell, F. *Acc. Chem. Res.* **1988**, *21*, 456–463.
10. Matthews, W.; Bares, J.; Bartmess, J. *J. Am. Chem. Soc.* **1975**, *97*, 7006–7014.
11. Bordwell, F.; Vanier, N.; Matthews, W. *J. Am. Chem. Soc.* **1975**, *97*, 7160–7162.
12. Régis, G.; Emmanuel, M.; Elyane, K. A.; Terrier, F. *J. Org. Chem.* **2003**, *68*, 6566–6570.
13. Hendrickson, J.; Skipper, P. L. *Tetrahedron* **1976**, *32*, 1627–1635.
14. Hendrickson, J.; Bair, K.; Bergeron, R.; Giga, A.; Skipper, P.; Sternbach, D.; Wareing, J. *Org. Preparations & Procedures Int.* **1977**, *9*, 173–207.
15. Hendrickson, J.; Judelson, D. *Synthesis* **1984**, 320–322.
16. (a) Langlois, B.; Billard, T.; Mulatier, J.; Yezeguelian, C. *J. Fluorine Chem.* **2007**,

- 128, 851–856; (b) Cao, H.-P.; Chen, Q.-Y. *J. Fluorine Chem.* **2007**, *128*, 1187–1190.
17. Hendrickson, J.; Giga, A.; Wareing, A. *J. Am. Chem. Soc.* **1974**, *96*, 2275–2276.
18. Hartgraves, G.; Burton, D. *CHIM OGGI.* **2009**, *27*, 27–30
19. (a) Hendrickson, J.; Bair, K. W. *J. Org. Chem.* **1977**, *42*, 3876–3878; (b) Hendrickson, J.; Bergeron, R. *Tetrahedron Lett.* **1973**, *46*, 4607–4610.
20. Hendrickson, J.; Sternbach, D.; Bari, K. W. *Acc. Chem. Res.* **1977**, *10*, 306–312.
21. Hendrickson, J.; Bair, K.; Keenhn, P. M. *J. Org. Chem.* **1977**, *42*, 2935–2936.
22. Eugene, F.; Langlois, B.; Laurent, E. *J. Fluorine Chem.* **1994**, *66*, 301–309.
23. Hrdina, A. H. I. Preliminary Investigation of a Catalytic Tsuji-Trost Reaction of β -Sulfonyl Esters. Bs.C. dissertation, Carleton University, Ottawa, ON, 2008
24. Kühnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; Martínez del Campo, T.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem.* **2007**, *119*, 7205–7208.
25. For recent reviews on donor-acceptor cyclopropanes, see: (a) Lebold, T.P.; Kerr, M. A. *Pure App. Chem.* 2010, *82*, 1797–1812; (b) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061–3071.
26. Dellaria, J. F.; Nordeen, C.; Swett, L. R. *Synth. Commun.* **1986**, *16*, 1043–1048.
27. Wagner, R.; Morre, J. *J. Am. Chem. Soc.* **1950**, *72*, 2884–2887.
28. Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2006**, *47*, 4707–4710.
29. For two examples of cyclic α -perhalosulfonyl ketones exhibiting keto-enol tautomerism, see: (a) Kobayashi, Y.; Yoshida, T.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *20*, 3865–3866; (b) Wagner, R.; Morre, J. *J. Am. Chem. Soc.* **1950**, *72*, 2884–2887.

30. (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233-4236; (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure App. Chem.* **1981**, *53*, 1109-1127.
31. Myers, A.; Yang, B.; Chen, H.; McKinstry, L.; Kopecky, D.; Gleason, J. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.
32. Russel, Al. E.; Popik, V. V. Ethyl Diazoacetate in *e-EROS Encyclopedia of Reagents for Organic Synthesis* [Online]; Wiley, Posted Online September 17, 2007. <http://onlinelibrary.wiley.com/o/eros/articles/re056/frame.html> (accessed on November 10, 2011).
33. (a) Okazaki, R.; Tokitoh, N. Trimethylsulfonium Iodide in *e-EROS Encyclopedia of Reagents for Organic Synthesis* [Online]; Wiley, Posted Online April 15, 2001. http://onlinelibrary.wiley.com/o/eros/articles/rt350/pdf_fs.html (accessed on November 24, 2011); (b) Ng, J. S.; Liu, C.; Aggarwal, V. K.; Winn, C. L. Dimethylsulfoxonium Methylide in *e-EROS Encyclopedia of Reagents for Organic Synthesis* [Online]; Wiley, Posted Online April 15, 2006. http://onlinelibrary.wiley.com/o/eros/articles/rd385/pdf_fs.html (accessed on November 24, 2011).
34. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
35. Verena, S.; Davoust, M.; Lemarle, M.; Lohler, J.; Santos, J. S. de O.; Metzner, P.; Brlere, J. *Org. Lett.* **2007**, *9*, 1745-1748.
36. Vloon, W. J.; Kruk, C.; Pandit, U. K.; Hofs, H. P.; McVie, J. G. *Org. Lett.* **2007**, *9*, 1745-1748.
37. (a) Weaver W. E., Whaley W. M. *J. Am. Chem. Soc.* **1947**, *69*, 515-516; (b)

- Swensen A. D., Weaver W. E.: *J. Am. Chem. Soc.* **1948**, *70*, 4060-4061; (c)
Pospisil, J.; Potacek, M. *Tetrahedron* **2007**, *63*, 337-346.
38. Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976-4985.
39. Gathergood, N.; Garcia, M. T.; Scammells, P. *Green Chem.* **2004**, *6*, 166-175.
40. Kobayashi, Y.; Yoshida, T.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *20*, 3865-3866.
41. Hanack, M.; Wilhelm, B.; Subramanian, L. R. *Synthesis* **1988**, 592-595.
42. Kong, H.; Gill, M.; Hrdina, A.; Crichton, J.; Manthorpe, J. *Submitted*.
43. (a) Nobelprize.org. *The Nobel Prize in Chemistry 2010*.
http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/ (accessed
November 2011); (b) Suzuki, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6722-6737; (c)
Negishi, E. *Angew. Chem. Int. Ed.* **2011**, *50*, 6738,-6764
44. (a) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422; (b) Trost, B.
M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2943.
45. Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199-3202.
46. Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**,
102, 6381-6384.
47. Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*,
1846-1913.
48. (a) Tsuda, T.; Tokai, M.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 421-426;
(b) Tsuda, T.; Tokai, M.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 5216-
5221.
49. Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113-4115.
50. Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044-15045.

51. (a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847; (b) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357.
52. Chattopadhyay, K.; Jana, R.; Day, V. W.; Douglas, J. T.; Tunge, J. A. *Org. Lett.* **2010**, *12*, 3042–3045.
53. Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988–2995.
54. Imao, D.; Itoi, A.; Yamazaki, A.; Shirakura, M.; Ohtoshi, R.; Ogata, K.; Ohmori, Y.; Ohta, T.; Ito, Y. *J. Org. Chem.* **2007**, *72*, 1652–1658.
55. (a) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843.; (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793–1796.
56. (a) Dübner, F.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 379–38.; (b) Dübner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233–9237; (c) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426–2428.
57. (a) Trost, B.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104–1105; (b) Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416–10417.
58. (a) Jones, G. L.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1995**, *34*, 462–464; (b) Pretot, R.; Lloyd-Jones, G.; Pfaltz, A. *Pure Appl. Chem.* **1998**, *70*, 1035–1040.
59. (a) Evans, P. A.; Kennedy, L. J. *J. Am. Chem. Soc.* **2001**, *123*, 1234–1235; (b) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974–8975.
60. Helmchen, G. N.; Dahnz, A.; Dubon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675–691.
61. Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461–1475.

62. (a) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529–3532; (b) Polet, D.; Alexakis, A. *Org. Lett.* **2005**, *7*, 1621–1624.
63. (a) Lipowsky, G.; Helmchen, G. N. *Chem. Commun.* **2004**, 116–117; (b) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 4595–4597; (c) Dahnz, A.; Helmchen, G. *Synlett* **2006**, 697–700; (d) Förster, S.; Tverskoy, O.; Helmchen, G. *Synlett* **2008**, 2803–2806; (e) Gnamm, C.; Förster, S.; Miller, N.; Brödner, K.; Helmchen, G. *Synlett* **2007**, 2007, 790–794; (f) Bartels, B.; Yebra, C. G.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 1097–1103; (g) Streiff, S.; Welter, C.; Schelwies, M.; Lipowsky, G.; Miller, N.; Helmchen, G. *Chem. Commun.* **2005**, 2957–2959.
64. Liu, W.-B.; Zheng, S.-C.; He, H.; Zhao, X.-M.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2009**, 6604–6606.
65. Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192–17193.
66. (a) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741–742; (b) Barterls, B.; Yebra, C. G.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569–2586; (c) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. N. *Chem. Commun.* **2004**, 896–897; (d) Welter, C.; Dahnz, A.; Brunner, B.; Streiff, S.; Dübon, P.; Helmchen, G. *Org. Lett.* **2005**, *7*, 1239–1242.
67. (a) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164–15165; (b) Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093–1096; (c) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272–14273.
68. (a) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426–

- 3427; (b) Shu, C.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 4794–4797.
69. Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6204–6207.
70. (a) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882–7883; (b) Evans, P. A.; Leahy, D. K.; Andrews, W. J.; Uraguchi, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4788–4791.
71. Madrahimov, S. T.; Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 7228–7229.
72. Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506–15514.
73. He, H.; Zheng, X.-J.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 4339–4341.
74. Gill, M. A.; Manthorpe, J. M. *Synth. Commun.* *In press.*
75. Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8971–8983.
76. Hatcher, M.; Posner, G. *Tetrahedron Lett.* **2002**, *43*, 5009–5012.