

Development of Palladium-Catalyzed Decarboxylative  
Allylation of Electron-Deficient Sulfones: Method  
Development and Mechanistic Studies

by

Monica Anne Gill

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

Doctor of Philosophy

in

Chemistry

Carleton University  
Ottawa, Ontario

© 2015, Monica Anne Gill

## Abstract

Palladium-catalyzed decarboxylative allylation is a powerful method of carbon-carbon bond construction. This methodology relies on an electron-withdrawing group to promote the reaction. The use of sulfones in decarboxylative allylation has been explored using the trifluoromethylsulfonyl (triflyl) group, as well as the bis(3,5-trifluoromethyl)phenylsulfonyl (BTMP) group. These substrates are highly reactive at room temperature (triflyl) and 50 °C (BTMP sulfones). A detailed mechanistic study using deuterium-labelled substrates was performed to understand the origin of the protonation side-product. It was proposed that a  $\beta$ -hydride elimination from the  $\eta^1$  allyl on palladium could generate a palladium hydride intermediate along with an allene. Although small amounts of deuterium incorporation were observed in the protonated products, the proposed mechanism could not be the major pathway. Using isotopically labelled ligand, however, all protonation was suppressed. This suggests that the origin of the proton is actually from the ligand and that kinetic isotope effects may be responsible for inhibiting the protonation pathway with labelled ligand.

## **Acknowledgments**

I would like to thank Dr. Jeff Manthorpe for giving me the chance to pursue my PhD in his lab. I always appreciated Jeff's enthusiasm for organic chemistry as well as his vast knowledge of the subject. Some of my most fond lab memories are of group brainstorming at the chalkboard with Jeff and whoever else was in the lab at the time. During my time as a PhD student, I had the opportunity to train and mentor a large (18!) number of undergraduate researchers. In fact, three went on to pursue Master's degrees in the Manthorpe lab. It was very rewarding to watch as the students grew from inexperienced undergrads to very capable graduate students. Han Kong, you were both an excellent colleague and friend. John Palko, your enthusiasm was refreshing. Sam Shields, I'm proud of the scientist you've become.

Thank you to members of the DeRosa lab who unofficially adopted me into their group when I began and had no fellow graduate students in my lab. I value the friendship of both past and present members of that group. Also, thank you to members of the Miller lab, both past and present, who have been residents of the grad office 410. One never knows what is being discussed when one walks through the door, but you can be sure it's interesting, and probably hilarious. Thank you to members of the Wang lab, both past and present, for their generous loan of so many chemicals to our group over the years.

I would like to extend my thanks to Jim Logan for his expertise in fixing a wide array of electronics in our lab, as well as helping me out on occasion with my personal laptop. I'd also like to acknowledge the role of Peter Mosher in preventing

Steacie from simply imploding on itself at any given time. Thank you to Tanya and Susa in stores for always being friendly faces and being up for a chat. Also, a huge thanks to Ann Anderson and Chantelle Gravelle (and Marilyn Stock before that) for all of their administrative assistance over the years.

I would like to thank my former co-workers at BioVectra for their support of me over the years. I learned so much from all of you while working in research and development, and have never forgotten the lessons I learned while in industry. I am very grateful that I am able to continue to count you all amongst my friends.

My family has always been very supportive of my desire to pursue my PhD. Thank you to my mother Elaine, and my sister Angela for their patience, support and understanding during the past years. My late father, Patrick, always encouraged my curious nature, and I know that was a major contributor to my scientific career.

I would like to finish by acknowledging the huge role that my fiancé Vince has played in my life during my degree. The level of support that he has shown me and the sacrifices that he made so willingly so that I could complete the work I needed to do are nothing short of stunning. Whether it be cooking me meals or sitting with me in the lab until the wee hours of the morning, he did it without hesitation. Thank you from the bottom of my heart for believing in my abilities and having more faith in me than I ever had in myself.

## Table of Contents

Abstract .....	ii
Acknowledgments .....	iii
Table of Contents .....	v
List of Abbreviations .....	viii
List of Figures .....	xi
List of Schemes .....	xv
List of Tables .....	xix
Chapter 1 : Introduction to Metal-Catalyzed Decarboxylative Allylation .....	1
1.1 Metal-Catalyzed Cross-Coupling Reactions .....	1
1.2 Palladium-Catalyzed Allylation .....	2
1.2.1 Initial Discovery using Stoichiometric Palladium .....	2
1.2.2 Early Catalytic Allylation and Regiochemistry .....	3
1.2.3 Catalytic Enantioselective Allylation .....	4
1.3 Decarboxylative Variants .....	5
1.4 Stereoselective DcA .....	12
1.5 Applications of DcA in Total Synthesis .....	16
1.6 Mechanism of Metal-Catalyzed DcA .....	18
1.7 DcA with Non-Enolate Nucleophiles .....	25
1.8 Project Goals .....	25
Chapter 2 : Pd-Catalyzed Decarboxylative Allylation of $\alpha$ -Triflones .....	27
2.1 Introduction .....	27
2.2 Attempts at Expanding Substrate Scope .....	31
2.2.1 Preparation of Other Secondary Alkylolithiums .....	31
2.2.2 Andersen Sulfoxide Approach .....	34
2.2.3 Ruppert-Prakash Reagent .....	36
2.2.4 Disulfide Approach .....	37
2.2.5 Sequential Alkylation & Acylation .....	38
2.2.6 Insight Into Behavior of $\alpha$ -Triflyl Anions .....	40
2.3 Extending Substrate Scope (Allylic ester) .....	41
2.3.1 Substrate preparation .....	41

2.3.2 Reductive Cleavage of Homoallylic Triflone .....	42
2.4 Methylation of $\alpha$ -Triflyl Esters .....	43
2.5 Attempted Derivatization of Triflyl-Substituted Ambiphilic Alkenes .....	46
2.6 Radical trap work .....	49
2.6.1 Preparation of appropriate substrate .....	50
2.6.2 Attempts at radical and anionic cyclization of ambiphilic alkene .....	51
2.7 Contemporary Work .....	52
2.8 Experimental .....	54
Chapter 3 : Pd-Catalyzed Decarboxylative Allylation of BTMP Sulfones .....	64
3.1 Alternate Electron-Withdrawing Group .....	64
3.2 Synthetic Approach .....	65
3.3 Development of New Esterification Method .....	73
3.3.1 Reaction Optimization .....	73
3.3.2 Substrate Scope .....	77
3.4 Optimization of Oxidation .....	78
3.5 Optimization of Alkylation .....	81
3.6 Early DcA Studies .....	84
3.7 Optimization of DcA for dibenzyl substrate Pd <sub>2</sub> (dba) <sub>3</sub> .....	91
3.8 Issues with Pd <sub>2</sub> (dba) <sub>3</sub> and Investigation of Baird Catalyst .....	92
3.8.1 Incomplete dissociation of dibenzylidene acetone .....	93
3.8.2 Pd nanoparticles .....	95
3.8.3 Baird Catalyst .....	97
3.9 Re-Optimization of DcA for dibenzyl substrate with Baird Catalyst .....	97
3.10 Evaluation of Substrate Scope .....	101
3.11 Reductive Cleavage of Sulfones .....	103
3.12 Summary .....	103
3.11 Experimental .....	105
Chapter 4 : Mechanistic Studies .....	159
4.1 Introduction .....	159
4.2 Protonation .....	160
4.2.1 Literature Review of Protonation Examples .....	160

4.2.2 Allene Proposal .....	168
4.2.3 Preparation of Deuterium Labelled Substrates .....	170
4.2.4 Results of DcA on Isotopically Labelled Substrates .....	171
4.2.5 Revised Mechanistic Proposal .....	173
4.2.6 DcA Reactions on Mechanistic Probes with Baird Catalyst.....	175
4.2.7 Synthesis and Evaluation of $\alpha,\alpha$ -dimethyl- $d_3$ Mechanistic Probe .....	178
4.2.8 Summary.....	179
4.3 Palladium (I) Dimers and Carboxylation .....	179
4.4 Ligand C-H Activation Proposal .....	184
4.4.1 Use of $d_{15}$ -PPh <sub>3</sub> on unlabelled substrate.....	188
4.4.2 Proposed Mechanism .....	188
4.4.3 Implications of Proposed Mechanism.....	190
4.5 Thesis Conclusions .....	191
4.6 Experimental .....	192
Chapter 5 : Publications & Conference Presentations.....	203
Chapter 6 : References .....	205
Chapter 7 : Appendix – <sup>1</sup> H & <sup>13</sup> C NMR Spectra .....	217

## List of Abbreviations

AAA	- asymmetric allylic alkylation
Acac	- acetylacetonate
BINAP	- 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	- benzyl (-CH <sub>2</sub> Ph)
Boc <sub>2</sub> O	- di- <i>tert</i> -butyl dicarbonate
<i>n</i> -BuLi	- <i>n</i> -butyllithium
BTMP	- 3,5-bis(trifluoromethyl)phenyl
CAM	- ceric ammonium molybdate
DACH	- diaminocyclohexane
dba	- dibenzylidene acetone
DBB	- di- <i>tert</i> -butylbiphenyl
DcA	- decarboxylative allylation
DCC	- <i>N,N'</i> -dicyclohexylcarbodiimide
DCM	- dichloromethane (methylene chloride)
DME	- 1,2-dimethoxyethane
DMF	- <i>N,N</i> -dimethylformamide
DMSO	- dimethylsulfoxide
DFT	- density functional theory
DIBAL	- diisobutylaluminum hydride
DMAP	- 4-( <i>N,N</i> -dimethylamino)pyridine
dmdba	- 4,4'-dimethoxydibenzylidene acetone
DOSY	- diffusion ordered NMR spectroscopy

DPEphos	- bis[(2-diphenylphosphino)phenyl] ether
Dppb	- 1,4-bis(diphenylphosphino)butane
Dppf	- 1,1'-bis(diphenylphosphino)ferrocene
ee	- enantiomeric excess
eV	- electron volt
ESI	- electrospray ionization
HMPA	- hexamethylphosphoramide
HRMS	- high resolution mass spectrometry
ICP-MS	- inductively coupled plasma mass spectrometry
IR	- infrared spectroscopy
LDA	- lithium diisopropylamide
LDBB	- lithium di- <i>tert</i> -butylbiphenylide
MeO-BIPHEP	- (6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine)
MeCN	- acetonitrile
NHC	- N-heterocyclic carbene
NMR	- nuclear magnetic resonance
NOESY	- Nuclear Overhauser Effect Spectroscopy
PCC	- pyridinium chlorochromate
PHOX	- phosphinooxazoline
PMA	- phosphomolybdic acid
SEGPLIOS	- 5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
TBAF	- tetrabutylammonium fluoride
TBAT	- tetrabutylammonium difluorotriphenylsilicate

Tf	- triflyl
TFA	- trifluoroacetic acid
THF	- tetrahydrofuran
TLC	- thin layer chromatography
TMS	- trimethylsilyl
Ts	- <i>p</i> -toluenesulfonyl
XANTPHOS	- 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

## List of Figures

Figure 1.1. Generalized mechanism for Pd-catalyzed cross coupling. ....	1
Figure 1.2. Saegusa's proposed mechanism for Pd-catalyzed decarboxylative allylation. ....	8
Figure 1.3. Introduction of allyl enol carbonates for DcA by Tsuji. ....	11
Figure 1.4. DcA on 1,3-disubstituted allylic substrates by Tunge. ....	12
Figure 1.5. First report of enantioselective DcA from Tunge. ....	13
Figure 1.6. Stoltz's enantioselective DcA of allyl enol carbonates. ....	14
Figure 1.7. Enantioselective DcA using silyl enol ethers and allylic carbonates. ....	15
Figure 1.8. Comparison of stereomutative and stereoablative enantioconvergent catalysis. ....	16
Figure 1.9. Synthetic approach by Stoltz to (+)-elatol. ....	17
Figure 1.10. Synthetic approach by Stoltz to cyanthiwigins. ....	17
Figure 1.11. First step in DcA: Ionization of ester. ....	18
Figure 1.12. Mechanism of DcA for $\alpha,\alpha$ -disubstituted substrates. ....	20
Figure 1.13. DFT calculated transition states for reductive elimination in DcA of allyl enol carbonates. ....	21
Figure 1.14. Two potential mechanistic pathways for substrates with $\alpha$ protons. ....	24
Figure 1.15. Examples of DcA reactions with non-enolate nucleophiles. ....	25
Figure 2.1. Standard alkylation conditions were ineffective. ....	28
Figure 2.2. Variety of possible products from alkylation of $\alpha$ -triflylacetates. ....	28
Figure 2.3. Proposed acylation of known sec-butyl triflone anion. ....	29

Figure 2.4. Attempted generation of secondary alkyllithium reagents and subsequent acylation.....	32
Figure 2.5. Andersen's synthesis of enantioenriched sulfoxides. ....	34
Figure 2.6. Proposed route to $\alpha,\alpha$ -dialkylated substrates via trifloxide. ....	34
Figure 2.7. Attempts at acylation of secondary benzyl triflones.....	39
Figure 2.8. Dominant resonance structure for $\alpha$ -nitro and $\alpha$ -triflone carbanions.	40
Figure 2.9. Attempted cyclopropanation of ambiphilic alkenes.....	47
Figure 2.10. Unexpected products from attempted Corey-Chaykovsky cyclopropanation of ambiphilic alkenes. ....	48
Figure 2.11. Attempted nucleophile addition and hydrogenation of ambiphilic alkenes. ....	49
Figure 2.12. Attempted radical (top) and anionic (bottom) cyclization of ambiphilic alkene derivatives.....	52
Figure 2.13. Tunge's optimization of Pd-cat DcA for phenyl sulfones.....	52
Figure 3.1. Substrate scope for sulfide oxidation.....	80
Figure 3.2. Initial DcA reactions of BTMP sulfones.....	84
Figure 3.3. Structure of ligands used in screening.....	90
Figure 3.4. Effect of dba ligand on generation of active Pd(0) catalysts. ....	93
Figure 3.5. Mechanism of cross-coupling with and without dba.....	95
Figure 3.6. Structure of ligands used in ligand screening. ....	100
Figure 3.7. Substrate scope for BTMP sulfone DcA. ....	101
Figure 3.8. Substrates that yielded only protonated product. ....	102
Figure 4.1. Tsuji's Pd-catalyzed decarboxylative protonation. ....	160

Figure 4.2. Tsuji's proposed catalytic cycle for Pd-catalyzed decarboxylative protonation.....	161
Figure 4.3. Tsuji's Pd-catalyzed decarboxylative protonation of diallyl malonate esters.....	162
Figure 4.4. Tsuji's Pd-catalyzed decarboxylative protonation of mixed malonate esters.....	162
Figure 4.5. Stoltz's enantioselective Pd-catalyzed decarboxylative protonation. ....	164
Figure 4.6. Labelling experiment in Stoltz's Pd-catalyzed decarboxylative protonation.....	166
Figure 4.7. Homogeneous Pd-catalyzed decarboxylative protonation.....	167
Figure 4.8. Expected label distribution based on mechanistic proposal. ....	170
Figure 4.9. Synthesis of allyl-2-d mechanistic probe. ....	170
Figure 4.10. Synthesis of allyl-1,1-d <sub>2</sub> mechanistic probe. ....	171
Figure 4.11. Results of allyl 2-d mechanistic probe. ....	172
Figure 4.12. Results of allyl-1,1-d <sub>2</sub> mechanistic probe.....	173
Figure 4.13. Yamamoto's Pd-catalyzed hydrocarbonation of allenes. ....	173
Figure 4.14. Yamamoto's mechanistic proposals for hydrocarbonation of allenes. ....	174
Figure 4.15. Revised mechanistic proposal for generation of protonated product. ....	175
Figure 4.16 Results of allyl-1,1-d <sub>2</sub> mechanistic probe with Baird catalyst. ....	176
Figure 4.17 Results of allyl-2-d mechanistic probe with Baird catalyst. ....	177

Figure 4.18 Results of allyl-1,1,2,3,3-d <sub>5</sub> mechanistic probe with Baird catalyst	177
Figure 4.19. Preparation of mixed $\eta^1$ and $\eta^3$ - allyl Pd complexes by Hazari. ....	181
Figure 4.20. Carboxylation of Pd(I) dimers. ....	183
Figure 4.21. Improved synthesis of Pd(I) dimers. ....	183
Figure 4.22. Moissev's synthesis of Pd cluster compounds.....	184
Figure 4.23. Moissev's initial mechanistic proposal accounting for origin of proton. .....	185
Figure 4.24. Ortho-palladation of ligand. ....	186

## List of Schemes

Scheme 1.1. Generalized scheme of Pd-catalyzed decarboxylation. ....	2
Scheme 1.2. Seminal example of Pd-catalyzed allylation from Tsuji. ....	3
Scheme 1.3. First example of catalytic Pd allylation from Hata. ....	4
Scheme 1.4. First example of catalytic Pd allylation from Atkins. ....	4
Scheme 1.5. Introduction of asymmetric Pd-catalyzed allylation from Trost. ....	5
Scheme 1.6. Mechanism of thermal Claisen rearrangement. ....	5
Scheme 1.7. Control experiment by Saegusa to evaluate timing of decarboxylation in mechanism. ....	9
Scheme 1.8. Cross-over experiments by Saegusa. ....	9
Scheme 1.9. Tsuji's proposed mechanism for Pd-catalyzed decarboxylative allylation. ....	11
Scheme 1.10. Stoltz's stereoablative enantioconvergent DcA. ....	15
Scheme 1.11. Tsuji's proposed mechanism for DcA in substrates containing $\alpha$ protons. ....	22
Scheme 1.12. Control experiment assessing inner- versus outer-sphere mechanism. ....	22
Scheme 1.13. Fiaud & Aribi-Zouioueche's experiment evaluating inner- versus outer-sphere mechanisms. ....	23
Scheme 1.14. Tunge's coumain-based substrates with reverse diastereoselectivity. ....	23
Scheme 2.1. Synthesis of allyl $\alpha$ -triflylacetate and attempted DcA. ....	27
Scheme 2.2. Pd-catalyzed DcA on $\alpha,\alpha$ -disubstituted triflyl substrate. ....	30

Scheme 2.3. Generation of LDBB radical anion. ....	31
Scheme 2.4. Proposed isolation of alkyl triflones & subsequent deprotonation, acylation. ....	33
Scheme 2.5. Preparation of cyclohexyl triflinate. ....	35
Scheme 2.6. Unexpected formation of dialkyl sulfinates. ....	35
Scheme 2.7. Examples of trifluoromethyl leaving group. ....	36
Scheme 2.8. Attempted synthesis of $\alpha,\alpha$ -dialkyl substrates via thiocyanates. ....	37
Scheme 2.9. Attempted preparation of alkyl trifluoromethyl sulfides. ....	37
Scheme 2.10. Preparation of substituted benzyl triflones. ....	38
Scheme 2.11. Synthesis of $\alpha,\alpha$ -disubstituted substrate with allylic substitution. ....	41
Scheme 2.12. Pd-catalyzed DcA on allylic substituted substrate. ....	42
Scheme 2.13. Reductive cleavage of homoallylic triflone. ....	42
Scheme 2.14. Initial methylation of $\alpha$ -triflyl ester. ....	43
Scheme 2.15. Methylation of $\alpha$ -triflyl ethyl acetate. ....	44
Scheme 2.16. Attempted derivatization of ambiphilic alkene via Diels-Alder reaction. ....	47
Scheme 2.17. Proposed radical cyclization of ambiphilic alkene derivative. ....	49
Scheme 2.18. Use of 1,2,6-triolhexane as starting material for cyclization substrate. ....	50
Scheme 2.19. Preparation of $\alpha$ -triflyl ketone cyclization substrate. ....	50
Scheme 2.20. Methylation of $\alpha$ -triflyl ketone cyclization substrate. ....	51
Scheme 3.1. Najera's synthesis of $\alpha,\alpha$ -dialkylated BTMP sulfone esters. ....	64
Scheme 3.2. Mechanism for Newman-Kwart rearrangement. ....	65

Scheme 3.3. Synthetic route towards $\alpha$ -BTMP sulfonyl allyl esters.....	66
Scheme 3.4. Saponification of $\alpha$ -BTMP sulfone ethyl ester.....	68
Scheme 3.5. Attempted esterification via acyl chloride.....	69
Scheme 3.6. Mechanism of mixed anhydride formation, esterification and byproduct formation.....	72
Scheme 3.7. Synthesis of differentially substituted substrates.....	83
Scheme 3.8. Isolation of palladacyclobutane intermediate.....	87
Scheme 3.9. Use of Pd( $\eta^3$ -1-PhC <sub>3</sub> H <sub>4</sub> )( $\eta^5$ -C <sub>5</sub> H <sub>5</sub> ) <b>3.120</b> as Pd(0) pre-catalyst....	97
Scheme 3.10. Reductive cleavage of BTMP sulfone from homoallylic product.	103
Scheme 4.1. Isolation of unexpected 4th product from DcA of $\alpha,\alpha$ -dimethyl substrate.....	159
Scheme 4.2. Muzart's enantioselective Pd-catalyzed decarboxylative protonation. .....	163
Scheme 4.3. Muzart's proposed mechanism for enantioselective decarboxylative protonation.....	163
Scheme 4.4. Proposed catalytic cycle accounting for protonated & cyclopropanated products.....	168
Scheme 4.5. Proposed mechanism accounting for formation of protonated product.....	168
Scheme 4.6. Wendt's synthesis of allyl Pd-pincer complexes.....	169
Scheme 4.7. Synthesis of allyl-1,1,2,3,3-d <sub>5</sub> mechanistic probe.....	175
Scheme 4.8. Synthesis of $\alpha,\alpha$ -dimethyl-d <sub>3</sub> mechanistic probe.....	178
Scheme 4.9. Results of $\alpha,\alpha$ -dimethyl-d <sub>3</sub> mechanistic probe.....	178

Scheme 4.10. Wendt's carboxylation of allyl Pd-pincer complexes. ....	180
Scheme 4.11. Wendt's mechanistic proposal for carboxylation of allyl Pd-pincer complexes. ....	181
Scheme 4.12. Proposed pathway for thermal degradation to Pd(I) dimer. ....	182
Scheme 4.13. Mechanistic proposal for carboxylation from Hazari. ....	182
Scheme 4.14. Tautomeric equilibrium in Ru complexes with tertiary phosphine ligands. ....	186
Scheme 4.15. Facile ortho-platination from benzyne-Pt complex. ....	187
Scheme 4.16. ortho-platination of triphenylphosphine. ....	187
Scheme 4.17. Use of $d_{15}$ -PPh <sub>3</sub> to probe mechanism. ....	188
Scheme 4.18. Proposed mechanism accounting for origin of protonated product. ....	189

## List of Tables

Table 1.1. Saegusa's seminal report of intramolecular decarboxylative allylation.	7
Table 1.2. Tsuji's introduction of intramolecular decarboxylative allylation. ....	10
Table 2.1. Reaction optimization for $\alpha,\alpha$ -diakyl triflyl substrate. ....	30
Table 2.2. Substrate scope for methylation of $\alpha$ -triflyl amides. ....	44
Table 2.3. Substrate scope for methylation of $\alpha$ -triflyl ketones. ....	45
Table 3.1. Attempted transesterification with $\alpha$ -BTMP sulfone ethyl ester. ....	66
Table 3.2. Attempted transesterification with $\alpha$ -BTMP sulfide ethyl ester. ....	68
Table 3.3. Summary of attempted esterification via carboxylic acid. ....	70
Table 3.4. Optimization of esterification via mixed pivalic anhydride. ....	73
Table 3.5. Substrate scope of esterification via mixed pivalic anhydride formation (BTMP sulfides). ....	75
Table 3.6. Substrate scope of esterification via mixed pivalic anhydride formation (other carboxylic acids). ....	76
Table 3.7. Optimization of oxidation conditions. ....	78
Table 3.8. Substrate scope for dialkylation (identical substituents). ....	82
Table 3.9. Evaluation of effect of Pd : phosphine ratio. ....	84
Table 3.10. Ligand screening study for $\alpha,\alpha$ -dimethyl substrates. ....	89
Table 3.11. Evaluation of temperature and solvent with BINAP for $\alpha,\alpha$ -dimethyl substrate. ....	91
Table 3.12. Solvent screen for $\alpha,\alpha$ -dibenzyl substrate. ....	92
Table 3.13. Solvent screening results for DcA reaction using (1-cinnamyl)PdCp. ....	98

Table 3.14. Ligand screening results for (1-cinnamyl)PdCp in THF. ....	99
Table 4.1. Substrate scope of Stoltz's enantioselective protonation.....	165

## Chapter 1 : Introduction to Metal-Catalyzed Decarboxylative Allylation

### 1.1 Metal-Catalyzed Cross-Coupling Reactions

Efficient formation of carbon-carbon bonds is one of the most important transformations in synthetic organic chemistry. During the last 50 years, there has been tremendous growth in the field of metal-catalyzed cross-coupling, particularly with the use of palladium. This chemistry finds wide use in the pharmaceutical industry, the development of organic semi-conductors and in the petroleum industry.<sup>1</sup> In fact, the Nobel Prize in Chemistry in 2010 was awarded to Richard Heck, Ei-ichi Negishi and Akira Suzuki for their seminal contributions to this field.

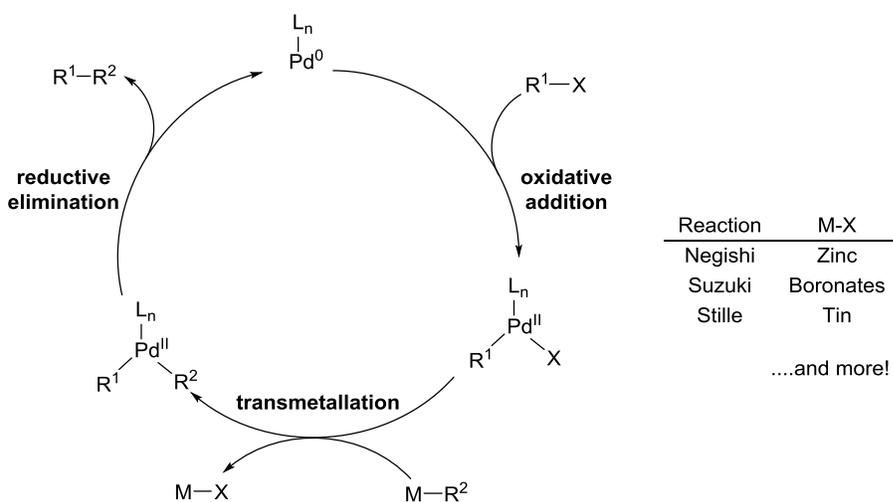
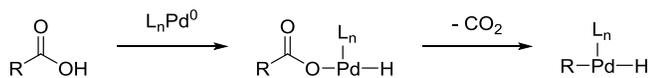


Figure 1.1. Generalized mechanism for Pd-catalyzed cross coupling.

Figure 1.1 shows a generalized mechanism for palladium-catalyzed cross coupling reactions. An organohalide  $R^1-X$  (or other leaving group) undergoes oxidative addition with a  $Pd^0$  catalyst to form a  $Pd^{II}$  intermediate. An organometallic species ( $M-R^2$ ) acts upon this  $Pd^{II}$  intermediate to give a transmetalation product. It is important to note that a stoichiometric amount of waste ( $M-X$ ) is formed during

the transmetallation step. Finally, the Pd<sup>0</sup> catalyst is regenerated by reductive elimination from the Pd<sup>II</sup> intermediate and the coupled product, R<sup>1</sup>-R<sup>2</sup>, is formed.

A wide variety of substrates and organometallic coupling partners have been developed. For example, the Stille reaction involves the coupling of an organohalide with an organotin compound. This is a rather robust reaction, but the generation of stoichiometric tin wastes is one of the major limitations of the Stille reaction. Decarboxylative processes are an interesting way to access organometallic species<sup>2</sup> since the initial process involves the relatively facile formation of a palladium-oxygen bond to form a Pd-carboxylate (Scheme 1.1). Decarboxylation yields the requisite organometallic species that is suitable for coupling reactions.



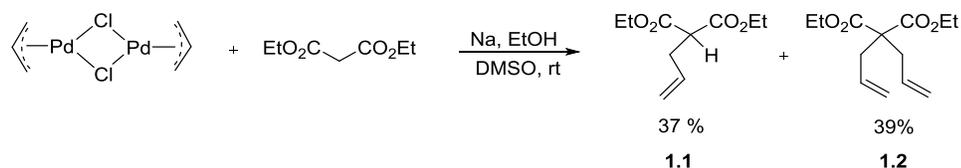
*Scheme 1.1. Generalized scheme of Pd-catalyzed decarboxylation.*

## 1.2 Palladium-Catalyzed Allylation

### 1.2.1 Initial Discovery using Stoichiometric Palladium

Tsuji's 1965 report of palladium-promoted allylation of stabilized nucleophiles (Scheme 1.2) marked the beginning of a rich area of research in synthetic organic chemistry.<sup>3</sup> Treatment of diethyl malonate with sodium ethoxide in DMSO in the presence of stoichiometric allyl palladium (II) dimer resulted in a mixture of monoallylated **1.1** (37%) and diallylated **1.2** (39%) products. During the course of the reaction, deposits of metallic palladium were observed. Ethyl

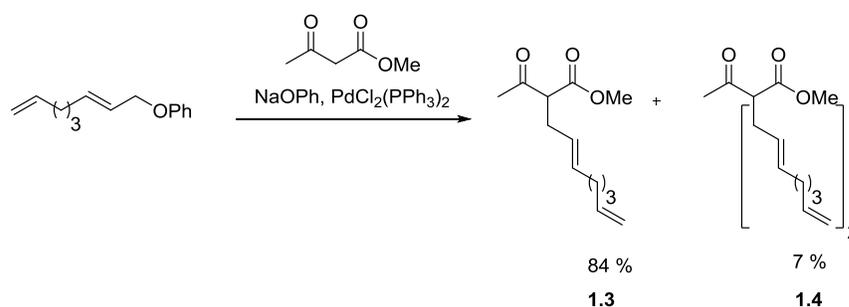
acetoacetate was also a viable allylation substrate, although yields and product distributions were not reported.



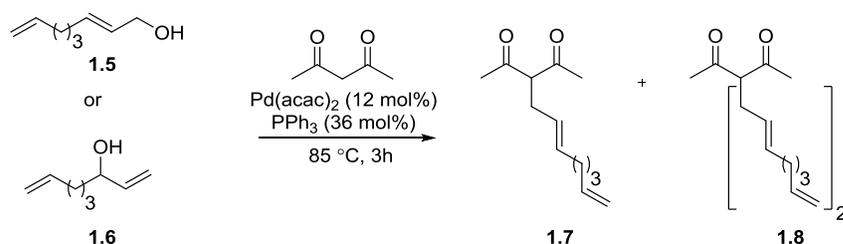
*Scheme 1.2. Seminal example of Pd-catalyzed allylation from Tsuji.*

### 1.2.2 Early Catalytic Allylation and Regiochemistry

In 1970, two separate examples of catalytic versions of Tsuji's allylation were reported. Hata and co-workers reported allylation of methyl acetoacetate using an allylic phenyl ether and catalytic bis(triphenylphosphine)palladium (II) chloride to yield **1.3** (Scheme 1.3). Only a small amount of diallylated product **1.4** was formed.<sup>4</sup> Later that same year, Atkins and co-workers reported allylation of acetylacetone (Scheme 1.4) employing allylic alcohols and catalytic Pd(acac)<sub>2</sub>.<sup>5</sup> When the reaction was performed with allyl alcohol, a product distribution of 73:27 mono to diallylated (**1.7** : **1.8**) was obtained. The use of either **1.5**, a primary allylic alcohol, or **1.6**, a secondary allylic alcohol, resulted in identical products. This result strongly suggested the presence of a  $\pi$ -allyl palladium intermediate in the catalytic cycle.



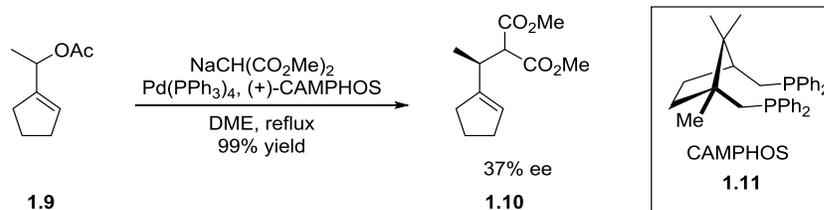
Scheme 1.3. First example of catalytic Pd allylation from Hata.



Scheme 1.4. First example of catalytic Pd allylation from Atkins.

### 1.2.3 Catalytic Enantioselective Allylation

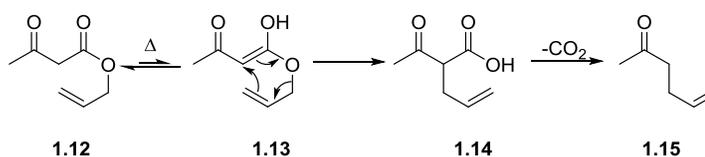
The first example of enantioselective palladium catalyzed allylation of stabilized nucleophiles was reported by Trost in 1977.<sup>6</sup> Allylic acetate **1.9** was employed with pre-formed dimethylmalonate sodium salt and catalytic tetrakis(triphenylphosphine)palladium(0) with a camphor derived diphosphine ligand **1.11** to yield enantioenriched **1.10** (Scheme 1.5). Only one regioisomer was produced; nucleophilic attack was not observed on the ring. The enantioselectivity was modest, but this report laid the groundwork for a plethora of research into palladium-catalyzed asymmetric allylic alkylation (AAA).<sup>7,8</sup>



Scheme 1.5. Introduction of asymmetric Pd-catalyzed allylation from Trost.

### 1.3 Decarboxylative Variants

In 1980, two groups independently reported development of a palladium-catalyzed *intramolecular* decarboxylative allylation (DcA) of allyl  $\beta$ -keto esters. These reactions could be thought of as variants on the Carroll rearrangement. The Carroll rearrangement is typically performed on allylic  $\beta$ -keto esters **1.12** at temperatures above 170 °C (Scheme 1.6). The enol tautomer of the ester moiety undergoes a 3,3-sigmatropic rearrangement to form **1.14**, followed by decarboxylation to yield homoallylic ketone **1.15**.



Scheme 1.6. Mechanism of thermal Claisen rearrangement.

Saegusa and co-workers reported the extension of allylation chemistry to allylic  $\beta$ -ketocarboxylates. Treatment of allylic  $\beta$ -ketocarboxylates with catalytic  $\text{Pd(PPh}_3)_4$  in DMF (Table 1.1) led to the corresponding homoallylic ketones in good to excellent yield for most substrates.<sup>9</sup> Overall, the process was an intramolecular decarboxylative allylation. The reaction conditions were remarkably mild, with

almost all reactions taking place at room temperature in 0.5 – 3 hours. The exception to this trend was the geranyl ester **1.20**, which required a temperature of 50 °C and gave a modest yield. Identical products were generated from substrates with methyl substitution in either the 1- or 3-position (**1.19** vs **1.18**) of the allylic ester, suggesting a  $\pi$ -allyl palladium intermediate. The authors noted a small amount of protonated product (**1.29**) when the substrate was  $\alpha,\alpha$ -dialkylated with an allyl group (**1.21**). However, when the analogous substrate with a propyl chain (**1.22**) was used, no protonated product was reported.

Table 1.1. Saegusa's seminal report of intramolecular decarboxylative allylation.

Substrate	Conditions	Product	% Yield
 1.16	n = 0, rt, 3 h n = 1, rt, 0.5 h	 1.23	n = 0, 88 n = 1, 96
 1.17	rt, 1 h	 1.24	92
 1.18	rt, 1 h	 1.25	75
 1.19	rt, 1 h	 1.26	72
 1.20	50 °C, 1 h	 1.27	39
 1.21	rt, 2 h	 1.28 + 1.29	67 + 9
 1.22	rt, 2 h	 1.30	67

The mechanism proposed by Saegusa and co-workers is shown in Figure 1.2. It was proposed that oxidative addition of the ester **1.40** to Pd(0) results in  $\pi$ -allyl, palladium-bound carboxylate species **1.41**. Decarboxylation of this species results in O-bound palladium-enolate **1.43**, which then attacked the electrophilic allyl group to give the desired product **1.45** and regenerate Pd(0).

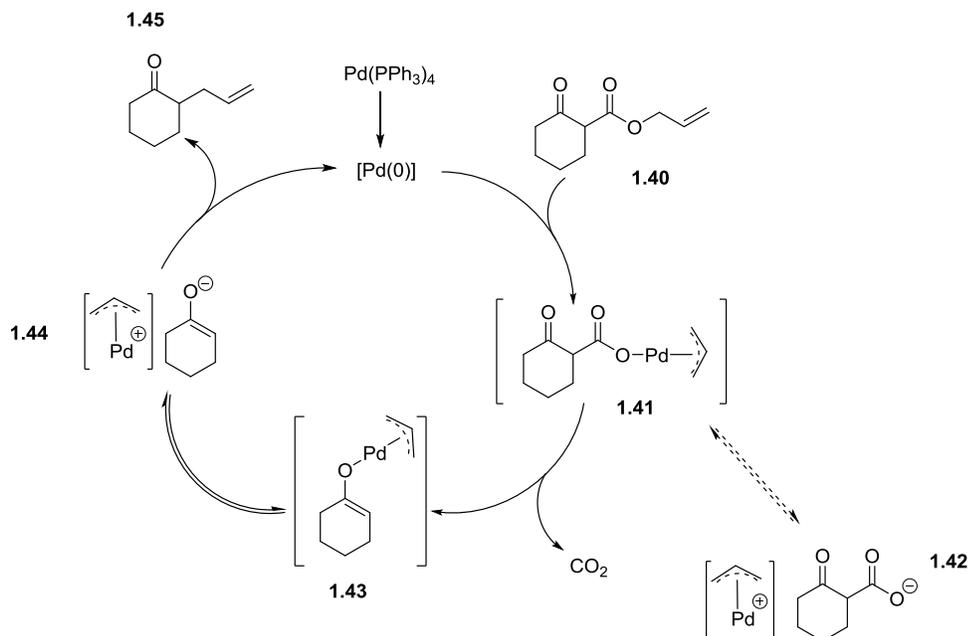
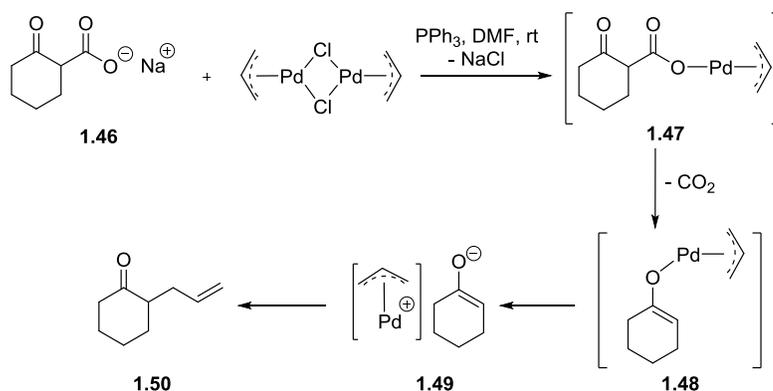


Figure 1.2. Saegusa's proposed mechanism for Pd-catalyzed decarboxylative allylation.

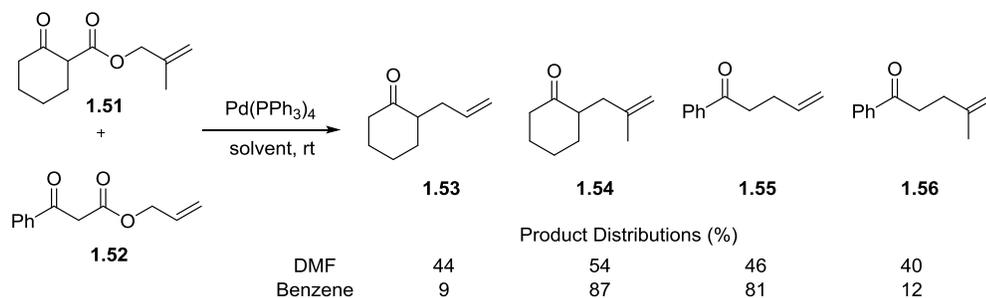
A control experiment was performed to understand the order in which decarboxylation took place. The sodium salt of a  $\beta$ -keto carboxylate **1.46** and palladium (II) chloride dimer were combined under the same reaction conditions as for the ester substrates (Scheme 1.7). The allylated ketone **1.50** was produced in 79%. The sodium salt does not undergo decarboxylation under the reaction

conditions unless the palladium complex is present. This evidence suggests that palladium-bound carboxylate **1.47** is an intermediate in the catalytic cycle.<sup>9</sup>



Scheme 1.7. Control experiment by Saegusa to evaluate timing of decarboxylation in mechanism.

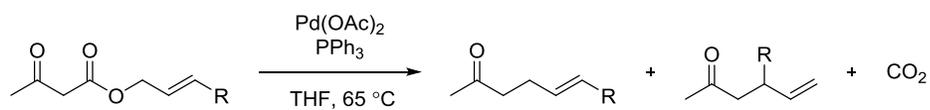
A series of cross-over experiments were also performed. The results are summarized in Scheme 1.8. When the reaction was carried out in DMF, cross-over was extensive. However, the same reaction in benzene resulted in minimal cross-over. This observation suggests that there may be differing, solvent-dependent mechanisms for this transformation. Alternatively, the lifetimes of some of the intermediates may be affected by the nature of the solvent.



Scheme 1.8. Cross-over experiments by Saegusa.

Almost simultaneously, Tsuji and co-workers reported on a similar transformation.<sup>10</sup> Allylic esters of acetoacetic acid were treated with palladium

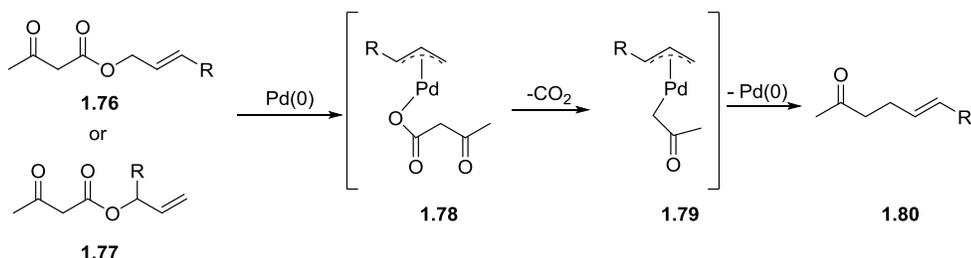
Table 1.2. Tsuji's introduction of intramolecular decarboxylative allylation.



Substrate	Product	% Yield
 1.57	 1.65	100
 1.58	 1.66	52
	 1.67	21
 1.59	 1.68	24
	 1.69	8 32 diallylated
 1.60	 1.70	40*
	 1.71	60*
 1.61	 1.72	100*
 1.62	 1.73	93*
 1.63	 1.74	56 3:1 E/Z
 1.64	 1.75	44

catalyst in THF to give homoallylic ketones with concomitant release of CO<sub>2</sub>. The reaction conditions differed slightly from those of Saegusa. A Pd(II) precursor was employed and THF was used as solvent at a higher temperature (Table 1.2). The time-course of the reaction appears similar, with reaction times ranging from 20

minutes to 4 hours. Tsuji's proposed mechanism is shown in Scheme 1.9. It emphasizes the  $\pi$ -allyl intermediate **1.78** and invokes a C-bound Pd enolate **1.79**.



Scheme 1.9. Tsuji's proposed mechanism for Pd-catalyzed decarboxylative allylation.

The substrate scope for decarboxylative allylation was expanded once more in 1983 when Tsuji reported the DcA of allyl enol carbonates.<sup>11</sup> It was envisioned that oxidative addition of the allyl carbonate moiety to Pd(0) would result in a similar O-bound enolate  $\pi$ -allyl palladium intermediate. In fact, these substrates were quite reactive; they would undergo DcA at 0 °C in DME (Figure 1.3).

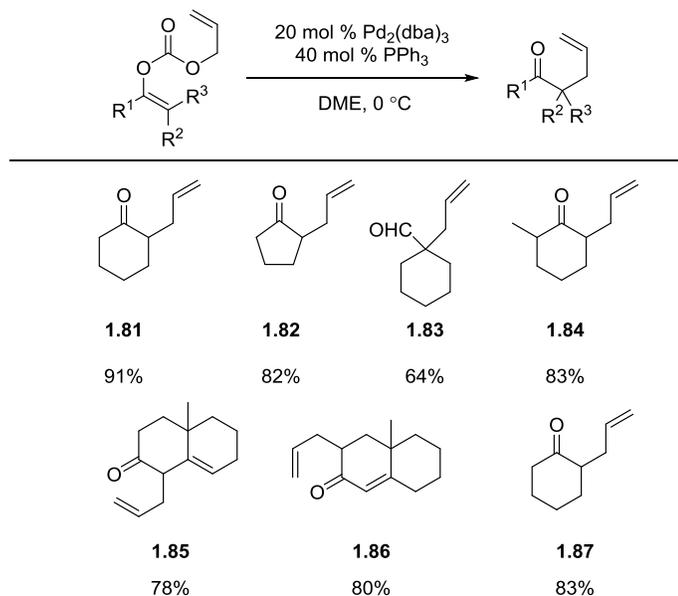


Figure 1.3. Introduction of allyl enol carbonates for DcA by Tsuji.

## 1.4 Stereoselective DcA

After the intense research into decarboxylative allylation processes in the 1980's, there was a waning of interest in this area. It wasn't until 2004 when two separate groups reported on Pd-catalyzed asymmetric DcA processes. Tunge's report on the DcA of  $\beta$ -keto esters first described the group's efforts in developing DcA on 1,3-disubstituted allyl fragments.<sup>12,13</sup> Using catalytic Pd(PPh<sub>3</sub>)<sub>4</sub> in benzene at room temperature, good to excellent yields were observed for all substrates (Figure 1.4). The reaction times for most substrates were quite long (15 – 48 h); however, the chalcone-based substrate (**1.88**) was high yielding (94%) in only 1 h.

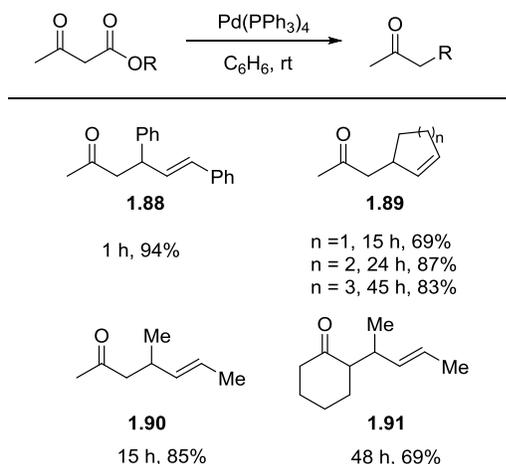


Figure 1.4. DcA on 1,3-disubstituted allylic substrates by Tunge.

Building on their success in developing suitable conditions for highly substituted allyl fragments, Tunge's group explored the possibility of rendering the process stereoselective. Using Trost's DACH phenyl ligand **1.99** and Pd<sub>2</sub>(dba)<sub>3</sub> as pre-catalyst, they obtained modest to excellent enantioselectivity (Figure 1.5).

Lowered enantioselectivity was observed when there was less conformational flexibility in the keto-fragment. For example, the cyclohexanone based substrate **1.94** resulted in only 54% ee, while the product from the analogous methyl ketone substrate **1.95** was isolated in 86% ee.

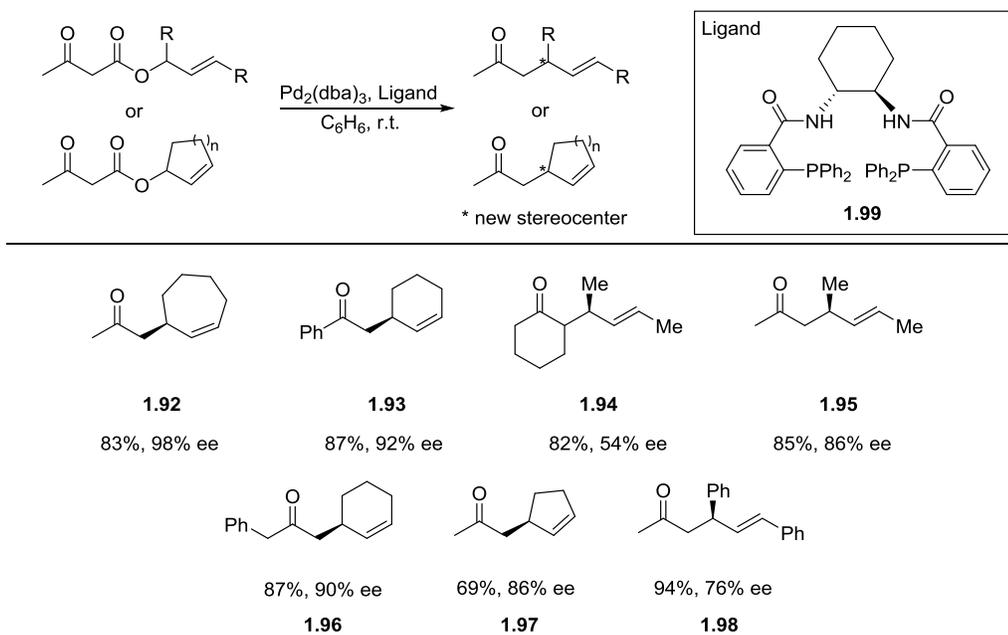


Figure 1.5. First report of enantioselective DcA from Tunge.

Later that same year, Stoltz reported asymmetric decarboxylative allylation using allyl enol carbonates and silyl enol ether substrates.<sup>14</sup> In contrast to Tunge's earlier report of enantioselective DcA, in which the new stereocenter was part of

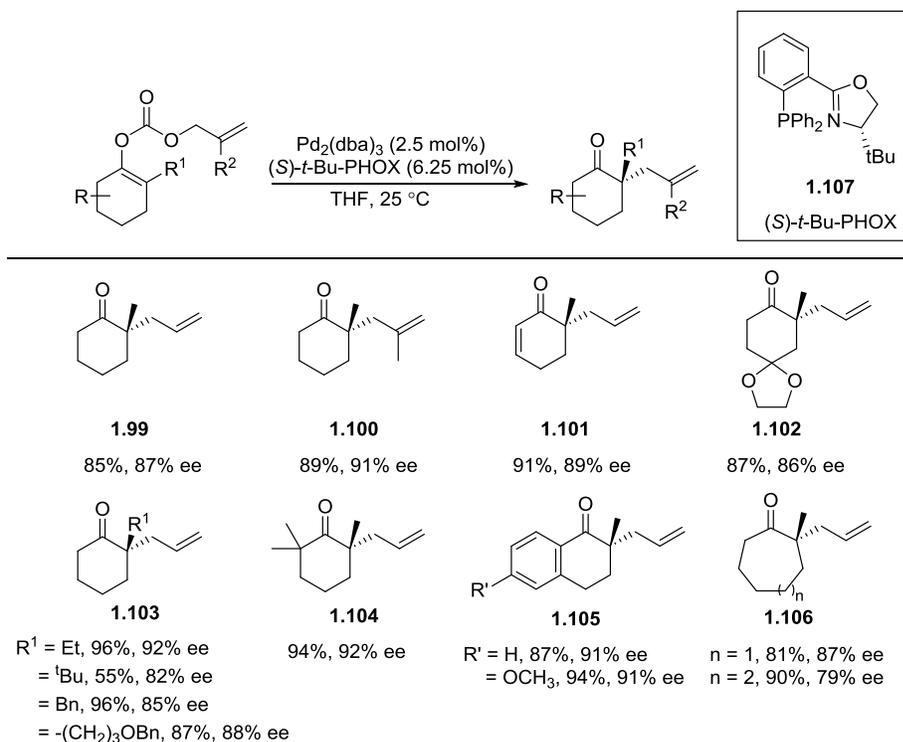


Figure 1.6. Stoltz's enantioselective DcA of allyl enol carbonates.

the allyl fragment,  $\beta$  to the keto functionality, Stoltz's substrates yielded a stereocenter in the  $\alpha$  position (Figure 1.6). The stereoselectivity was achieved using (S)-t-Bu-PHOX, a member of an oxazoline-based family of ligands derived from  $\alpha$ -amino acids (both natural and unnatural). A variety of 6-8 membered cycloalkanones and tetralones were successfully employed. Most examples used only a simple allyl group, with only one example of 2-substitution. In addition, Stoltz's group reported an analogous *intermolecular* asymmetric process in which silyl enol ethers reacted with allylic carbonates under similar catalytic conditions

(Figure 1.7). TBAT, an anhydrous fluoride source, generated the requisite enolate.

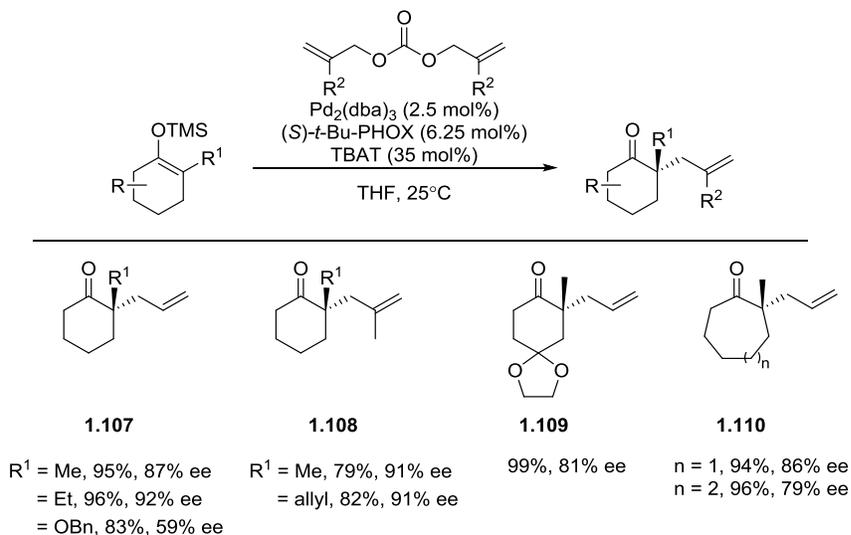
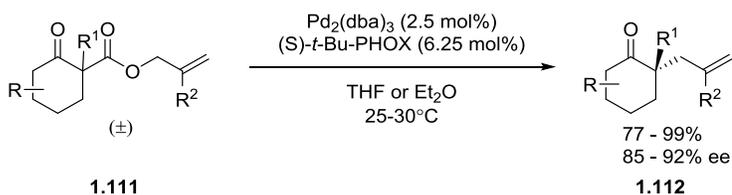


Figure 1.7. Enantioselective DcA using silyl enol ethers and allylic carbonates.

The next year, Stoltz reported on a third class of substrates that could undergo enantioselective DcA. Treatment of racemic quaternary  $\beta$ -keto esters under similar conditions to those used for allyl enol carbonates resulted in good



Scheme 1.10. Stoltz's stereoablative enantioconvergent DcA.

to excellent yields of highly enantioenriched products (Scheme 1.10). In general, racemic mixtures of substrates can only give high yields of products if there is possibility for a dynamic kinetic resolution. As shown in

Figure 1.8, so-called stereomutative enantioconvergent catalysis is possible when a rapid equilibration between enantiomers of starting material exists, and there is a difference between the rate of conversion of the two enantiomers to product. Interconversion of the quaternary centers in the racemic mixture is highly unlikely, therefore this process was conceptually different. Stoltz's group termed this process "stereoablative enantioconvergent catalysis"; a racemic mixture of starting materials converges to an achiral intermediate, then the enantioenriched ligand controls the stereoselectivity exclusively.

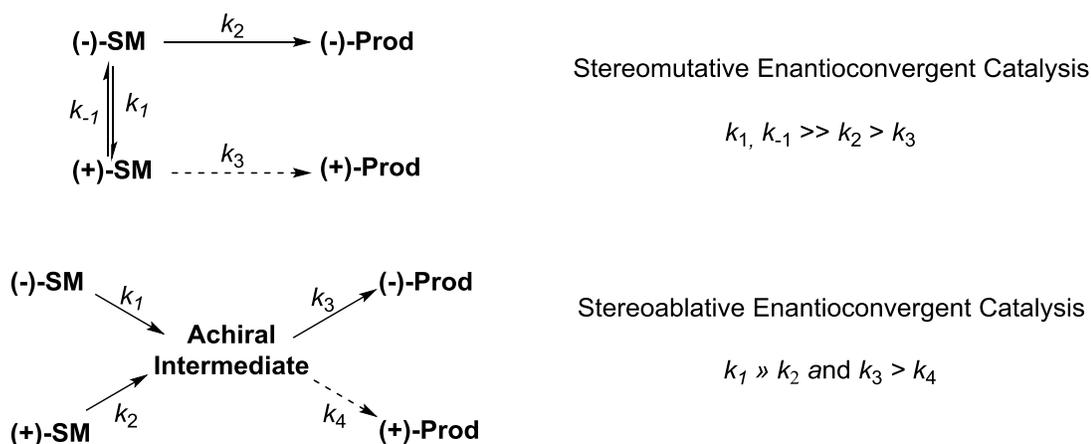


Figure 1.8. Comparison of stereomutative and stereoablative enantioconvergent catalysis.

## 1.5 Applications of DcA in Total Synthesis

Stoltz and co-workers applied their asymmetric decarboxylative allylation methodology to the total synthesis of the chamigrene family of natural products.<sup>15,16</sup> These are characterized by a spiro[5.5]undecane core in which the spiro-carbon is an all-carbon quaternary center. The short and efficient synthesis of (+)-elatol is shown in Figure 1.9. The substrate for the asymmetric

decarboxylative allylation was prepared in 4 steps from commercially available dimedone **1.113**. It was found that optimal yield and enantioselectivity was

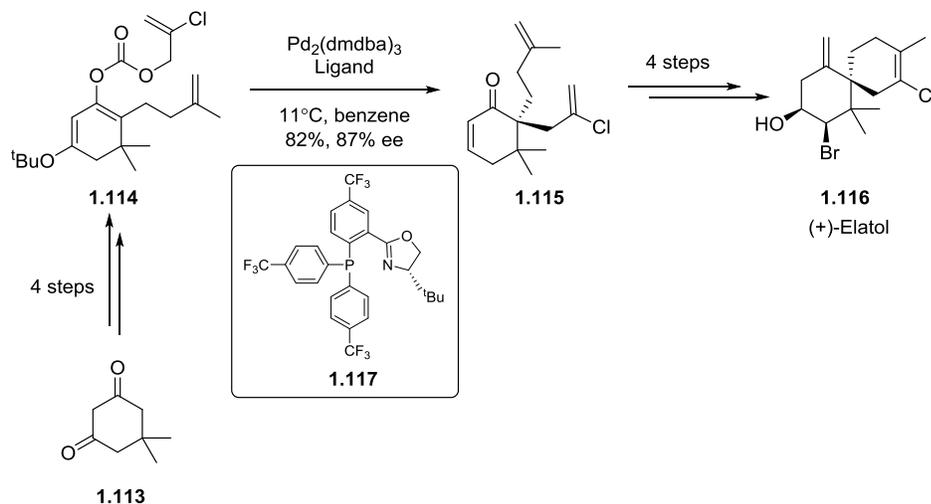


Figure 1.9. Synthetic approach by Stoltz to (+)-elatol.

obtained using  $\text{Pd}_2(\text{dmdba})_3$  (an analogue of  $\text{Pd}_2(\text{dba})_3$  using 3,5-dimethoxydibenzylidene acetone instead)<sup>17</sup> and an electron-deficient PHOX ligand analogue **1.117**. The product was isolated with 87% ee and was elaborated to (+)-elatol **1.116** in four additional steps.

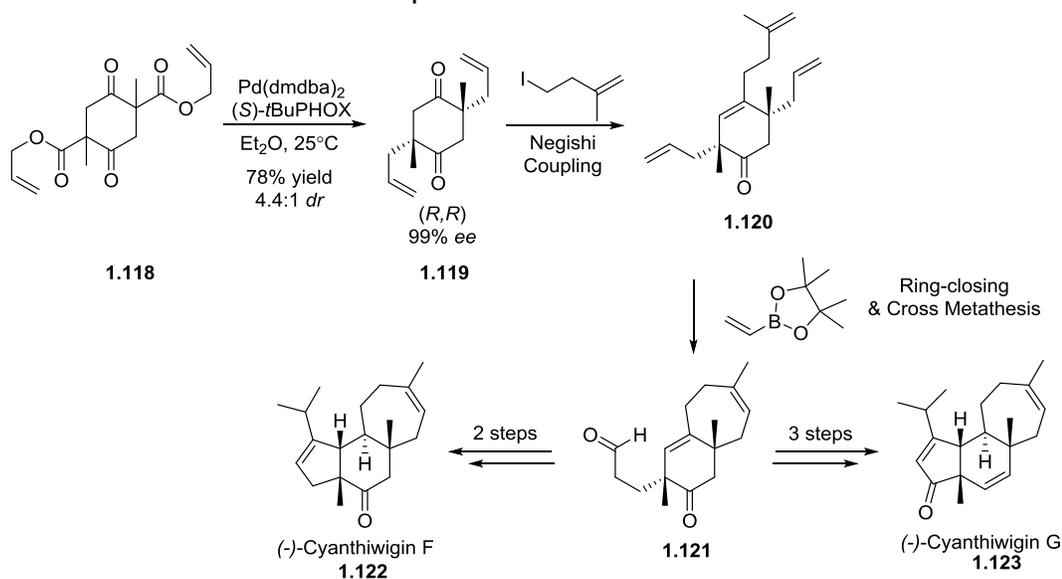


Figure 1.10. Synthetic approach by Stoltz to cyanthiwigins.

Taking advantage of the stereoablative enantioconvergent methodology developed in their group, Stoltz and Enquist Jr. reported on a remarkable transformation in Nature in 2008.<sup>18</sup> They found that a 1:1 mixture of racemic and meso diastereomers **1.118** could be cleanly converted to a single enantiomer in 99% ee, 78% yield using Pd-catalyzed DcA methodology. Using this methodology, they rapidly completed total syntheses of a number of members of the cyanthiwigin family, as illustrated in Figure 1.10.

### 1.6 Mechanism of Metal-Catalyzed DcA

Most mechanistic studies for intramolecular DcA has focused on enolate-based nucleophiles. This work was nicely summarized in Tunge's 2011 review on metal-catalyzed decarboxylative allylation.<sup>19</sup> Several important features will be highlighted in this section. Particular attention will be paid to apparent mechanistic differences occurring between  $\alpha,\alpha$ -dialkylated substrates and substrates containing  $\alpha$ -protons.

The first step in all proposed mechanisms is the Pd-promoted ionization of an allyl carboxylate or carbonate. The formation of a  $\pi$ -allyl palladium carboxylate ion pair (**1.125**) that is in equilibrium with a neutral  $\sigma$ -bound  $\eta^1$ -allyl complex (**1.126**)

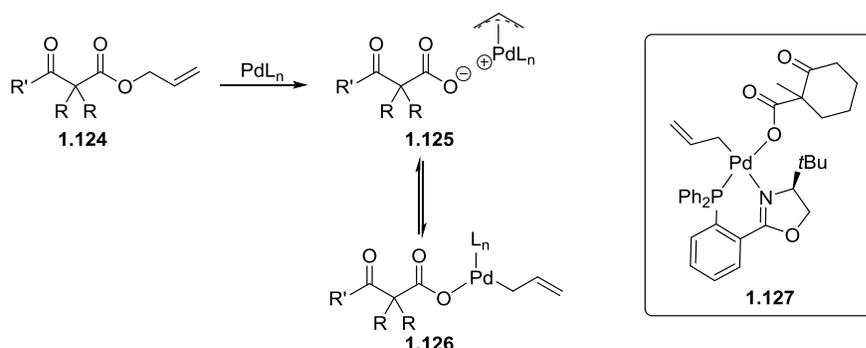


Figure 1.11. First step in DcA: Ionization of ester.

is proposed. Stoltz and Sherden provided substantial evidence for the existence of such a  $\sigma$ -bound  $\eta^1$ -allyl complex as part of the catalytic cycle with the isolation of a square-planar, 16 electron palladium complex (Figure 1.11).<sup>20</sup> This work was prompted by attempts at monitoring the Pd-catalyzed decarboxylative allylation reaction by <sup>31</sup>P NMR. Initially, two peaks due to free ligand and active catalyst were observed. A third peak began to form as the reaction proceeded, then disappeared completely by the end of the reaction. This peak was due to the carboxylate-bound product **1.127** that had been isolated and studied by X-ray crystallography.

Once the allyl ester is ionized, there are two main questions with respect to the mechanism of DcA. First, one must resolve the order of events in the mechanism. Does decarboxylation precede allylation or does the reverse occur? Second, does the allylation occur through an inner-sphere mechanism (enolate bound to Pd prior to reductive elimination) or via an outer-sphere mechanism (in which enolate directly attacks cationic  $\eta^3$ -allyl Pd). Several groups have explored these mechanistic questions over the last 30 years.

When one considers substrates in which there is  $\alpha,\alpha$ -disubstitution, it becomes obvious that it is not possible for allylation to occur prior to

decarboxylation. As illustrated with the example in Figure 1.12, allylation can't possibly take place until after decarboxylation. The site of allylation is quaternary all-carbon center until decarboxylation occurs. There are a variety of possible intermediates that could form after the decarboxylation event, and they could conceivably be in equilibrium with each other. An outer-sphere ion pair **1.130**, an inner-sphere O-enolate-bound Pd complex **1.131** and an inner-sphere C-enolate-

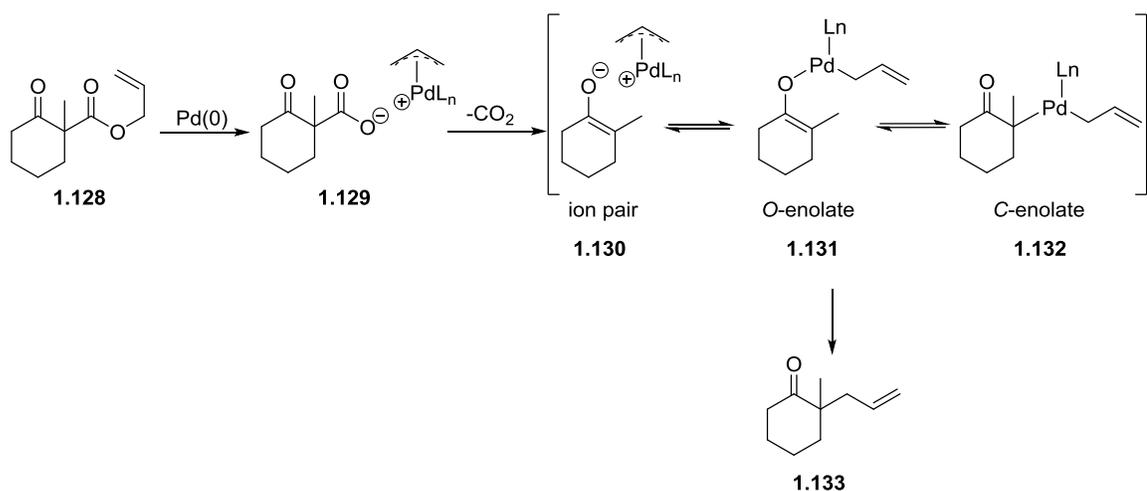


Figure 1.12. Mechanism of DcA for  $\alpha, \alpha$ -disubstituted substrates.

bound Pd complex **1.132** are all possible. These mechanistic possibilities are not easily distinguished.

A collaborative effort from Stoltz and Goddard examined the issue of inner-sphere versus outer-sphere processes with respect to decarboxylative allylation of

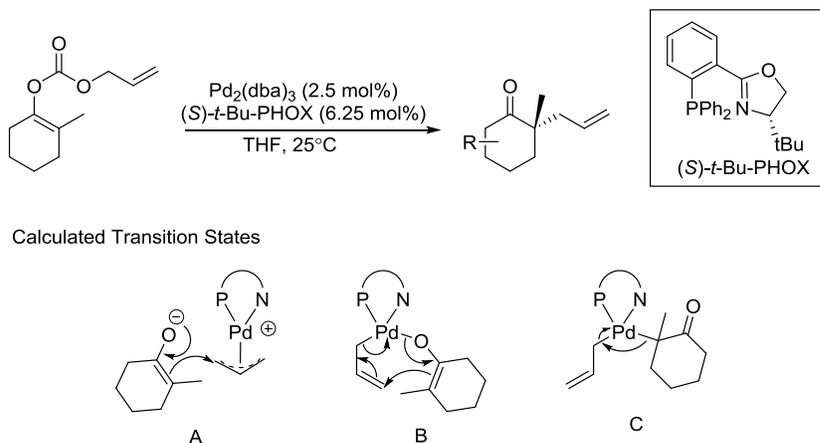
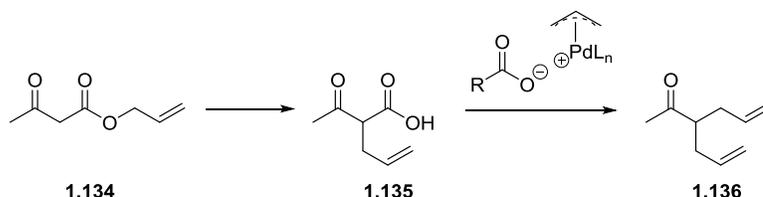


Figure 1.13. DFT calculated transition states for reductive elimination in DcA of allyl enol carbonates.

allyl enol carbonates.<sup>21,22</sup> Extensive DFT calculations were performed in an attempt to further understand this mechanism. Additionally, they wished to rationalize the good (79 – 92% ee) but never excellent (> 95% ee) enantioselectivities observed for this reaction. This is despite extensive optimization studies in the Stoltz group. In particular, they wanted to gain insight into the reductive elimination step and understand the nature of the enantioselectivity. DFT calculations were performed on both outer- and inner-sphere models. The energy difference between the outer-sphere transition state (**A**) and the somewhat unusual inner-sphere 7-membered transition state (**B**) is a mere 1.2 kcal/mol (Figure 1.13). The three-center reductive elimination transition state (**C**) based on C-bound enolate is 41 kcal/mol higher in energy than (**B**). In fact, in contrast to many experimental results suggesting outer-sphere

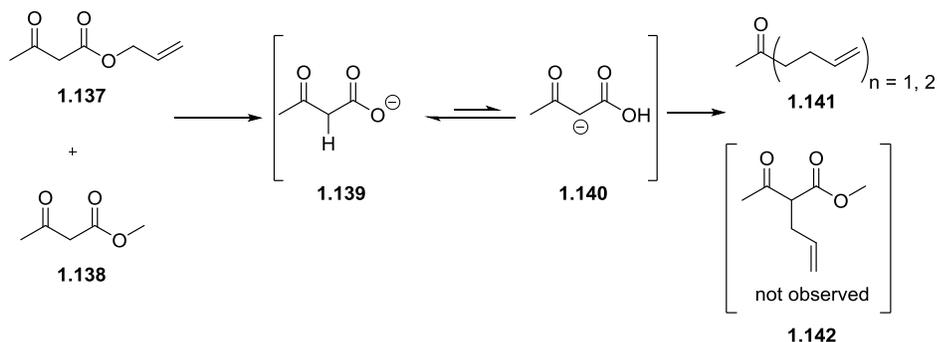
mechanisms, the results of three different computational schemes were all in agreement that inner-sphere pathways were lower in energy.

Substrates that contain  $\alpha$  protons are mechanistically less straightforward with respect to order of decarboxylation and allylation. Tsuji suggested in 1980 that allylation preceded decarboxylation, and that an intermediate allylated carboxylic



*Scheme 1.11. Tsuji's proposed mechanism for DcA in substrates containing  $\alpha$  protons.*

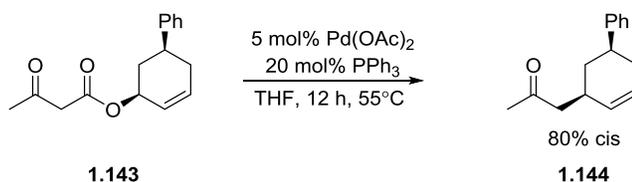
acid (**1.135**) was formed (Scheme 1.11).<sup>10</sup> This was rationalized by ionization of the allyl ester and subsequent proton transfer from  $\alpha$ -carbon to carboxylate oxygen. To evaluate if the proton transfer was inter- or intramolecular, an experiment was performed with equimolar quantities of allyl and methyl



*Scheme 1.12. Control experiment assessing inner- versus outer-sphere mechanism.*

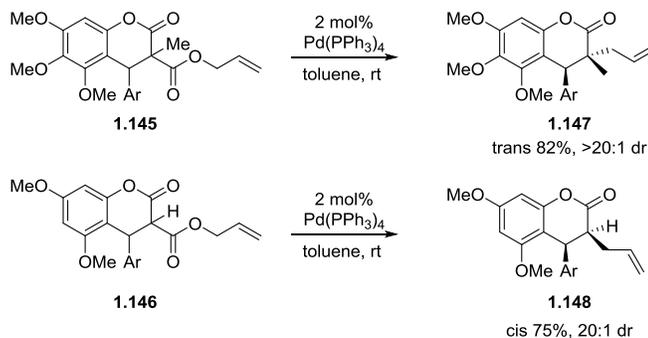
acetoacetate. If the proton transfer was intermolecular, it would be conceivable that methyl acetoacetate could be deprotonated and subsequently allylated. However, allylated methyl acetoacetate (**1.142**) was not observed (Scheme 1.12).

Fiaud and Aribi-Zouioueche studied the stereochemical outcome of substrates with  $\alpha$  protons present.<sup>23</sup> A highly diastereomerically pure allyl ester was prepared and subjected to DcA conditions, as shown in Scheme 1.13. The product was found to be 80% cis, suggesting that a double-inversion, outer-sphere mechanism is in operation. It was suggested that the reduction in diastereomeric purity could be attributed to epimerization of the starting material, or to a competing, inner-sphere process.



Scheme 1.13. Fiaud & Aribi-Zouioueche's experiment evaluating inner- versus outer-sphere mechanisms.

Tunge and co-workers observed a remarkable dependence of the  $\alpha$ -substitution in the stereochemical outcome of a DcA reaction.<sup>24</sup> While studying the DcA reaction on substituted coumarin substrates, it was found that those with  $\alpha,\alpha$ -dialkylation (**1.145**) yielded trans products with very high diastereoselectivity. Analogous substrates with one  $\alpha$  H (**1.146**) also gave products with high diastereoselectivity, however in the opposite sense (cis) (Scheme 1.14). This stereochemical trend is consistent across a variety of coumarin-based substrates.



Scheme 1.14. Tunge's coumarin-based substrates with reverse diastereoselectivity.

Epimerization of the starting material with  $\alpha$  protons was ruled out based on computational modelling results that suggested that the epimers were approximately equivalent in energy.

Two different mechanistic pathways were conceivable for the  $\alpha$ -protio substrates. As illustrated in Figure 1.14, decarboxylation takes place following ionization of the allyl ester in Path A. The stereochemistry determining step takes

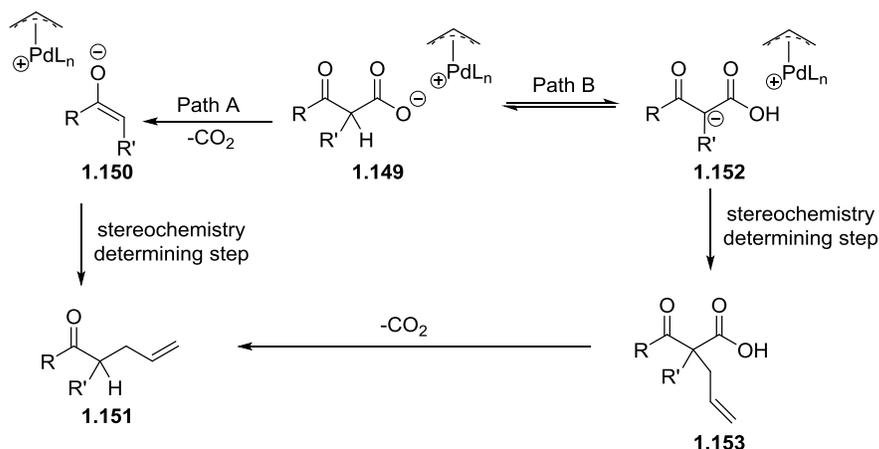


Figure 1.14. Two potential mechanistic pathways for substrates with  $\alpha$  protons.

place by allylation of the enolate. In Path B, however, a proton transfer step takes place to form the corresponding carboxylic acid after ionization. The crucial difference in Path B is that the stereochemical determining step takes place prior to decarboxylation. Tunge *et al.* were able to differentiate between the two potential pathways by monitoring the reaction by <sup>1</sup>H NMR. In d<sub>8</sub>-toluene, a broad peak consistent in chemical shift with a carboxylic acid begins to appear at t = 15 min, reaches a maximum intensity at t = 33 min and is no longer observed by t = 43 min. This piece of experimental data correlates strongly with the Path B mechanism.

## 1.7 DcA with Non-Enolate Nucleophiles

The array of suitable substrates for DcA has been expanded greatly in the last 30 years. While enolate-based nucleophiles formed the basis of much of the initial reaction development, a wide array of nucleophiles have now been successfully used in DcA reactions. Figure 1.15 features a selection of electron-

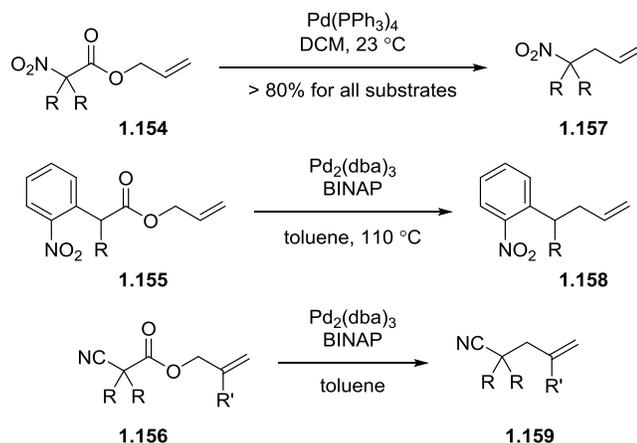


Figure 1.15. Examples of DcA reactions with non-enolate nucleophiles.

poor, non-enolate nucleophiles developed in the Tunge group. Nitroalkanes **1.154** were readily allylated at room temperature,<sup>25</sup> while nitrobenzene derivatives **1.155** were allylated at higher temperatures and then could be reduced to the corresponding substituted anilines.<sup>26</sup> Finally, DcA was facilitated by the use of the nitrile electron-withdrawing group on substrates such as **1.156**.<sup>27</sup>

## 1.8 Project Goals

Our initial research goal was to evaluate the feasibility of adapting Tsuji-Trost decarboxylative allylation substrates to include  $\beta$ -sulfone esters. In this way, the sulfone could facilitate the decarboxylative allylation, but then be easily cleaved under a variety of conditions. One could thus envision that the sulfone would act

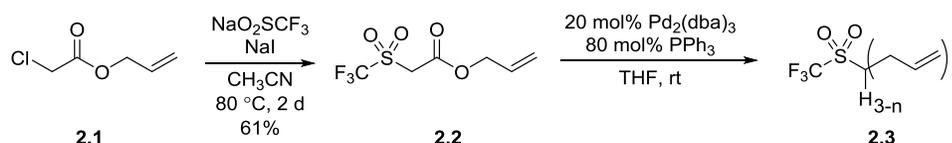
as an alkane synthon. Additionally, these substrates would be interesting from a mechanistic perspective; it would not be possible to form O-enolates, as in  $\beta$ -keto esters.

## Chapter 2 : Pd-Catalyzed Decarboxylative Allylation of $\alpha$ -Triflones

### 2.1 Introduction

*Note: Experiments in Section 2.1 were carried out by Amy Hrdina in the Manthorpe research group, as part of her B.Sc. Honours thesis (2007-08).<sup>28</sup>*

We chose to investigate  $\alpha$ -trifluoromethylsulfonyl allyl esters (the adjective trifluoromethanesulfonyl is commonly abbreviated to *triflyl* and trifluoromethyl sulfones are often termed *triflones*) as the initial substrates for DcA. Since its introduction by Sheppard in the 1960's,<sup>29</sup> the triflone group has been widely used as a powerful electron withdrawing group. It was envisioned that the electron withdrawing capability of the triflyl group might enhance the reactivity. The initial



Scheme 2.1. Synthesis of allyl  $\alpha$ -triflylacetate and attempted DcA.

substrate, allyl  $\alpha$ -triflylacetate **2.2**, was prepared in modest yield via treatment of allyl chloroacetate **2.1** with the Langlois reagent (sodium trifluoromethanesulfinate) and sodium iodide in refluxing acetonitrile for 48 hours.<sup>30</sup> A solution of allyl  $\alpha$ -triflylacetate **2.2** in THF was combined with catalytic Pd(0), generated from  $\text{Pd}_2(\text{dba})_3$  and  $\text{PPh}_3$  in a 1:2 Pd:P ratio. This initial DcA reaction generated a mixture of mono-, di- and tri-allylated products **2.3** (Scheme 2.1).

Poly-allylation is not unusual in Pd-catalyzed decarboxylative allylation reactions.<sup>31,32</sup> This issue is easily resolved by using substrates with substitution in the  $\alpha$ -position. The most straightforward synthetic sequence to obtain a dialkylated

substrate was to deprotonate allyl  $\alpha$ -triflylacetate and quench the resultant anion with an alkylating agent. It was found, however, that this seemingly trivial

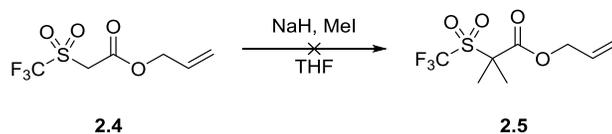


Figure 2.1. Standard alkylation conditions were ineffective.

transformation was not possible using a deprotonation/electrophilic quench sequence (Figure 2.1). Triflyl acetate esters are relatively strong C-H acids – ethyl triflylacetate has a  $\text{pK}_a$  of 6.4 in DMSO.<sup>33</sup> To put this value in context, it is useful to consider that, in DMSO, acetic acid has a  $\text{pK}_a$  of 12.6.<sup>34,35</sup> Additional issues arise from the presence of halide anions, the by-product of alkylation. Langlois and co-workers have identified the by-products and the mechanistic pathways by which these are formed.<sup>30</sup> As illustrated in Figure 2.2, nucleophilic attack by the halide on

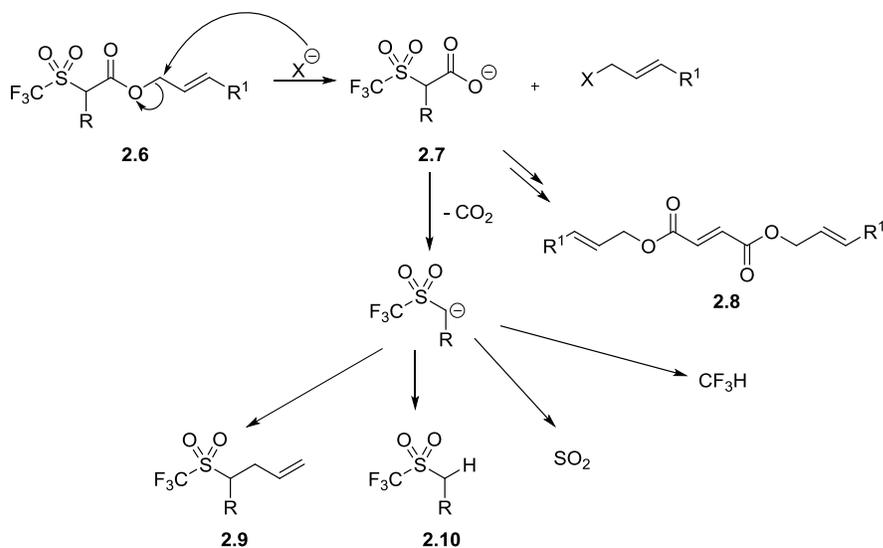


Figure 2.2. Variety of possible products from alkylation of  $\alpha$ -triflylacetates.

**2.6** leads to carboxylate **2.7** which may spontaneously decarboxylate leading to potential products **2.9** and **2.10** or further react to yield fumarate ester **2.8**.

We were intrigued by a report from Hendrickson and Bair that explored the use of reagents such as triflic anhydride and *N*-phenyl triflimide (**2.11**) for the synthesis of triflones.<sup>36,37</sup> The treatment of triflic anhydride with *sec*-butyllithium yielded 43% *sec*-butyl triflone **2.18**, as well as an unreported amount of ditriflated

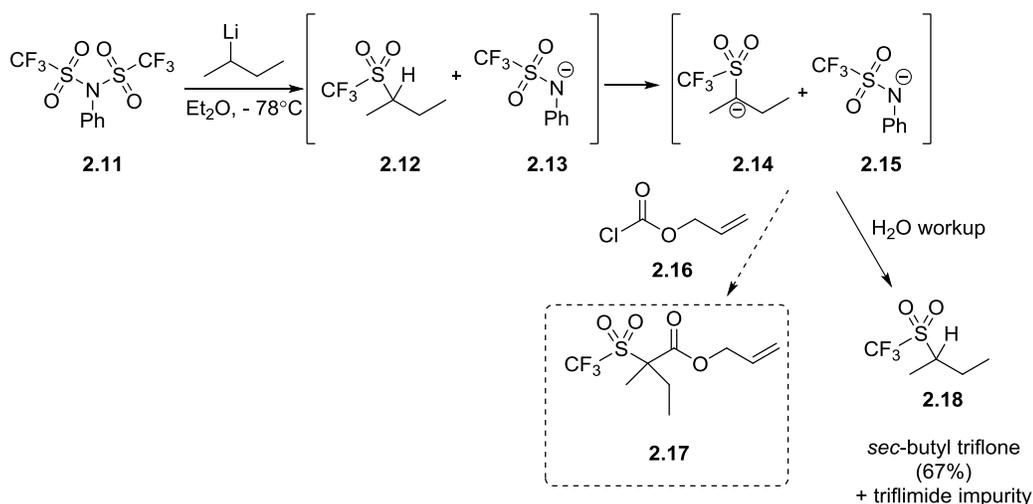
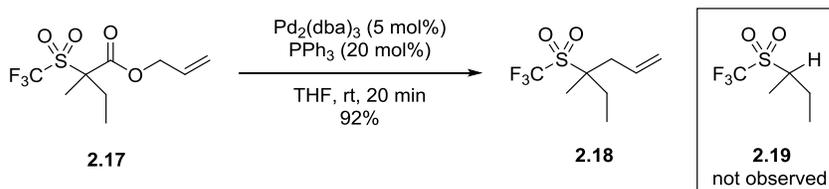


Figure 2.3. Proposed acylation of known *sec*-butyl triflone anion.

product. However, the reaction of *N*-phenyl triflimide with *sec*-butyllithium gave a 67% yield of *sec*-butyl triflone **2.18** and no traces of ditriflated products. As illustrated in Figure 2.3, the *sec*-butyl triflone anion **2.14** was quenched by water upon work-up. It was postulated that the *sec*-butyl triflone anion could be intercepted instead by an acylating agent, such as allyl chloroformate **2.16**. In this way, *α,α*-dialkylated allyl triflylacetate **2.17** could be prepared in a one-pot process.

Indeed, **2.17** was successfully prepared in 62%, after flash chromatography to remove the acylated triflimide impurity. Treatment of the disubstituted triflone with 5 mol% Pd<sub>2</sub>(dba)<sub>3</sub> and PPh<sub>3</sub> (such that there was a 2:1 phosphine: Pd ratio) in THF resulted in the desired homoallylic triflone in high yield at room temperature

in less than 30 minutes (Scheme 2.2). The reaction was very clean; the only other components observed in the crude  $^1\text{H}$  NMR spectrum were dba and  $\text{PPh}_3$ . Most notably, none



Scheme 2.2. Pd-catalyzed DcA on  $\alpha,\alpha$ -disubstituted triflyl substrate.

of the troublesome protonated product (**2.19**) often obtained in these types of reactions was observed. The catalytic conditions were optimized by evaluating the influence of solvent, temperature and catalyst loading (Table 2.1). The reaction was found to be largely solvent independent. Good yields and short reaction times were achieved with  $\text{Et}_2\text{O}$ , toluene, DCM and THF with 10 mol% Pd, although THF was the only solvent that resulted in > 90% yield. Dropping the catalyst loading to 5 mol% in THF resulted in a small reduction in yield (entry 7). Reactivity and yield were very similar when catalyst loading in THF was dropped even further to 2 mol%

Table 2.1. Reaction optimization for  $\alpha,\alpha$ -diakyl triflyl substrate.

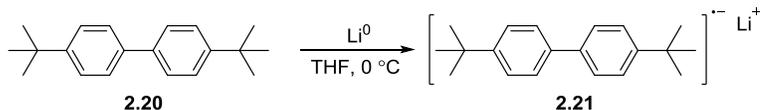
Entry	Solvent	Temperature	Mol% Pd	Time	Yield (%)
1	$\text{Et}_2\text{O}$	rt	10	20 min	89
2	PhMe	rt	10	20 min	86
3	PhMe	rt	2	17 h	7
4	DCM	rt	10	20 min	84
5	DCM	rt	2	6 h	11
6	THF	rt	10	20 min	92
7	THF	rt	5	30 min	79
8	THF	rt	2	30 min	78
9	THF	0 °C	2	30 min	61

(entry 8). Even at 0 °C with 2 mol% Pd in THF, a yield of 61% was obtained (entry 9).

## 2.2 Attempts at Expanding Substrate Scope

### 2.2.1 Preparation of Other Secondary Alkylolithiums

Attention was turned to preparing additional substrates. The main challenge with the preparation of additional substrates was the lack of commercially available secondary alkylolithium reagents. At the time of this work, only *sec*-butyl and *iso*-propyllithium were commercially available. We elected to synthesize various secondary alkylolithium compounds by reaction with lithium di-*tert*-butyl biphenylide (LDBB (**2.21**); sometimes known as Freeman's reagent). LDBB is generated by



Scheme 2.3. Generation of LDBB radical anion.

treatment of di-*tert*-butylbiphenyl **2.20** in THF at 0 °C (Scheme 2.3) The resultant bright blue solution is generally used immediately, as LDBB is unstable at temperatures above 0 °C. There was precedence from the original reports from Freeman that secondary alkyl halides could be converted to the corresponding alkylolithium compounds using LDBB.<sup>38,39</sup>

As illustrated in Figure 2.4, three different secondary alkyl halides were utilized in the initial studies. Solutions of alkyl halide in THF were cooled to  $-78\text{ }^{\circ}\text{C}$ , then freshly prepared LDBB was added. The distinct blue-green color of LDBB did not persist; a red/yellow color was generated depending on the alkyl halide used. The presumed anion solution was then added to a solution of PhNTf<sub>2</sub>, warmed to room temperature, then quenched using allyl chloroformate. The crude <sup>1</sup>H NMR

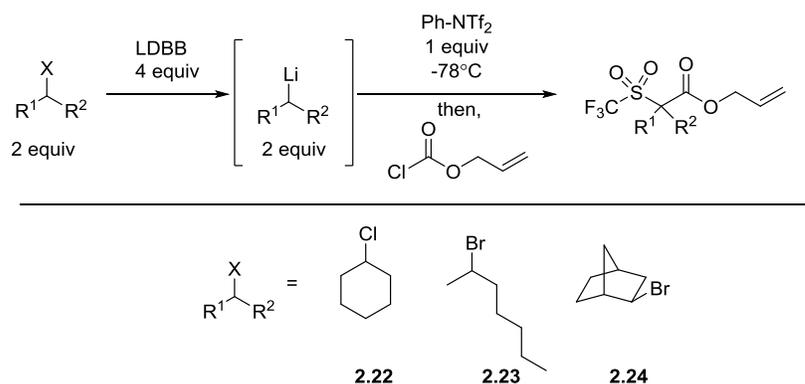


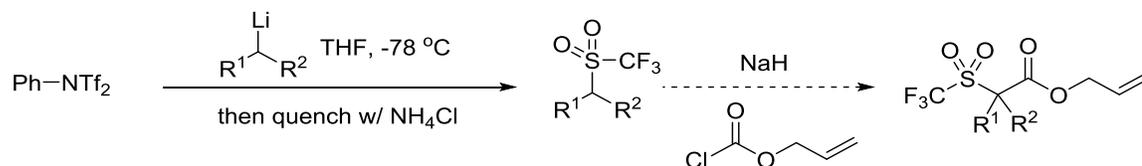
Figure 2.4. Attempted generation of secondary alkyllithium reagents and subsequent acylation.

spectral analyses of these reactions suggested that there was *some* product formation, however there were many other impurities. The most notable impurities were super-stoichiometric quantities of di-*tert* butylbiphenyl and the N-acyl sulfonamide byproduct. These impurities proved exceptionally difficult to remove and hindered our ability to assess the success of the reaction. DBB is typically quite easy to remove via column chromatography due to its low polarity. Unfortunately, the triflone compounds would often co-elute with DBB, even in 100% hexane.

In an attempt to ease purification, Comins reagent was used in place of *N*-phenyl triflimide. While structurally Comins reagent is structurally similar to *N*-

phenyl triflimide, it was designed to be more reactive.<sup>40</sup> The electron-deficient pyridine ring was anticipated to withdraw electron density from the triflimide group, thereby increasing its electrophilicity. Additionally, removal of the by-product was possible via acidic aqueous workup. The same series of experiments were performed with Comins reagent as in Figure 2.4. Disappointingly, the results were similar to the use of N-phenyl triflimide.

We then elected to change the above one-pot process into two distinct steps, with a purification in between steps. Rather than quenching with allyl chloroformate, the reaction was simply quenched with saturated aqueous ammonium chloride, to produce the alkyl triflone. Deprotonation of the alkyl triflone with sodium hydride, and addition of allyl chloroformate would then produce the desired product (Scheme 2.4).



*Scheme 2.4. Proposed isolation of alkyl triflones & subsequent deprotonation, acylation.*

Unfortunately, purification of the alkyl triflones proved to be equally challenging due to their exceptional non-polarity. Column purification of the material was further complicated by the fact that the alkyl triflones could be observed by TLC only at high concentrations. All standard visualization methods (UV, I<sub>2</sub>, PMA, CAM, KMnO<sub>4</sub>, *p*-anisaldehyde) and non-standard methods (chromic acid, H<sub>2</sub>SO<sub>4</sub> in MeOH) were unable to detect product in column fractions. The secondary alkyl lithium approach was ultimately abandoned.

## 2.2.2 Andersen Sulfoxide Approach

An attractive source of nucleophilic carbon compounds are Grignard reagents. There are many more commercially available secondary Grignard reagents than lithium compounds. Unfortunately, Grignard reagents have been shown not to react with N-phenyl triflimide.<sup>36,41</sup> We opted to investigate the

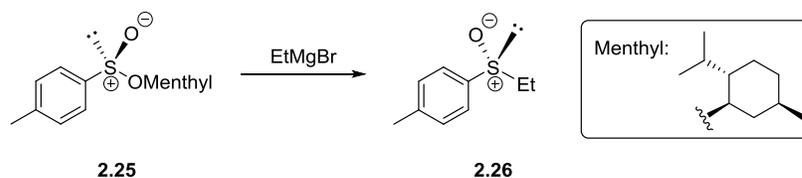


Figure 2.5. Andersen's synthesis of enantioenriched sulfoxides.

reaction of trifluoromethane *sulfonates* with Grignard reagents in analogy to the Andersen approach to sulfoxides.<sup>42,43</sup> This methodology, first reported in 1962, found that diastereomerically pure sulfinate esters of menthol **2.25** could be cleanly converted to enantiomerically pure sulfoxides **2.26** with the opposite stereochemistry via treatment with a Grignard reagent, as shown in Figure 2.5.

We envisioned that we could use Grignard reagents with triflate compound **2.27** to give the corresponding “trifloxide” **2.28**. These “trifloxides” could then be oxidized to give alkyl triflates. A subsequent deprotonation and quench

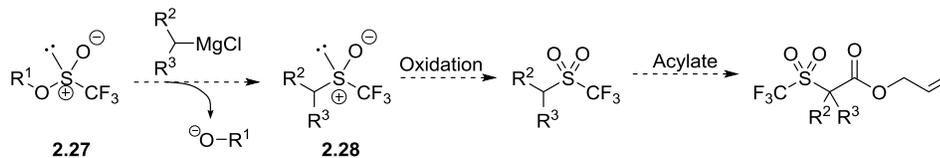
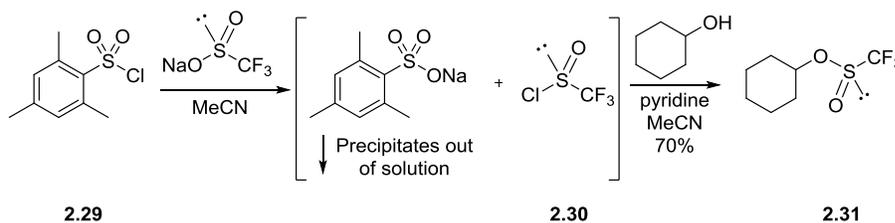


Figure 2.6. Proposed route to  $\alpha,\alpha$ -dialkylated substrates via trifloxide.

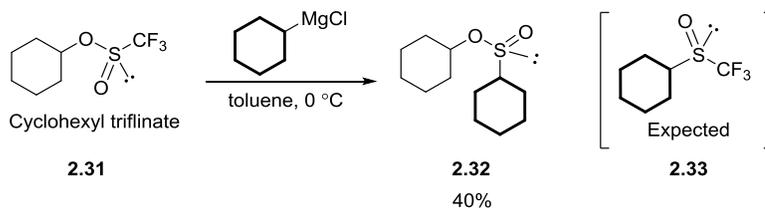
with an acylating agent, such as allyl chloroformate, could conceivably give the desired substrate (Figure 2.6). The cyclohexyl group was chosen as a simple test

substrate. Cyclohexanol was treated with  $\text{CF}_3\text{SOCl}$  (generated *in situ* from mesitylenesulfonyl chloride and sodium triflate<sup>44</sup> and used immediately in the next step) to give cyclohexyl triflate **2.31** in 70% yield (Scheme 2.5).



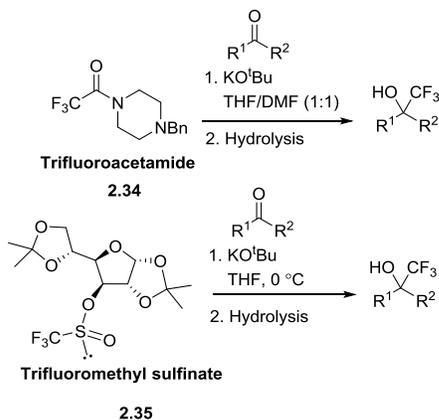
*Scheme 2.5. Preparation of cyclohexyl triflate.*

Compound **2.31** was treated with 2.5 equivalents of cyclohexylmagnesium chloride in the key step (Scheme 2.6). It was anticipated that the cyclohexyl alkoxide would act as the leaving group in this nucleophilic attack, however the observed product indicates that  $-\text{CF}_3$  acted as the leaving group to give cyclohexyl cyclohexanesulfinate **2.32**. This unexpected behaviour, although rare, has



*Scheme 2.6. Unexpected formation of dialkyl sulfinate.*

literature precedence.<sup>45,46</sup> Langlois and co-workers had developed a trifluoroacetamide reagent that acted as a source of nucleophilic  $\text{CF}_3$  in the presence of potassium *tert*-butoxide. In an attempt to improve the electrophilicity



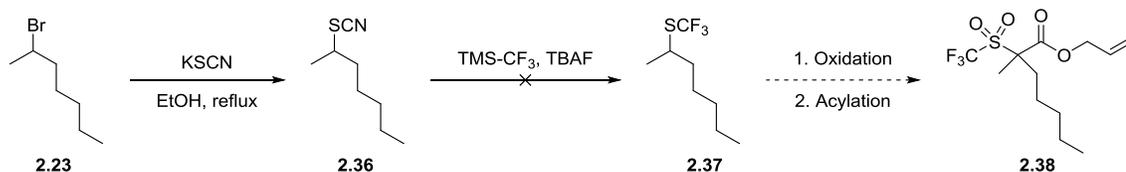
*Scheme 2.7. Examples of trifluoromethyl leaving group.*

of the reagent, they prepared a series of trifluoromethyl sulfinate analogues (**2.34-2.35**). Shown in Scheme 2.7, the trifluoromethyl sulfinate derivative of diacetone glucose was successful in expelling  $^-CF_3$  via an unstable tetrahedral intermediate. While this was the goal of Langlois *et al.*, this was unhelpful in the goal of synthesizing the desired triflyl acetate substrates. This approach was ultimately abandoned.

### 2.2.3 Ruppert-Prakash Reagent

The Ruppert-Prakash reagent (trifluoromethyl trimethylsilane, TMS- $CF_3$ ) is a source of nucleophilic  $CF_3^-$ . Though first reported by Ruppert in 1984,<sup>47</sup> its use was later popularized by Prakash.<sup>48</sup> We have explored two possible uses of this reagent in an effort to prepare the desired dialkylated triflone substrates. Langlois reported that thiocyanates may be converted to the corresponding trifluoromethyl sulfides using the Ruppert-Prakash reagent and catalytic TBAF.<sup>49,50</sup> It was envisioned that the sulfide product could then be oxidized to give the corresponding alkyl triflone. Simple deprotonation and quenching with allyl

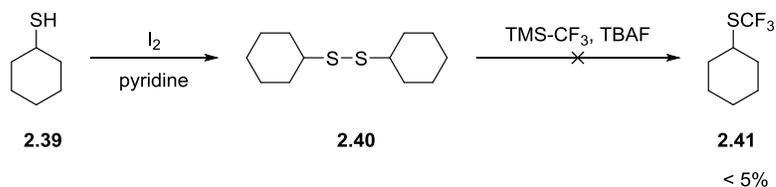
chloroformate was anticipated to give the desired product. As illustrated in Scheme 2.8, 2-bromoheptane was converted cleanly to 2-thiocyanoheptane in refluxing ethanol. The treatment of the thiocyanate with TMS-CF<sub>3</sub> and catalytic TBAF, however, did not give satisfactory results. A complex mixture of starting material and unidentified impurities was isolated. This approach was ultimately abandoned.



Scheme 2.8. Attempted synthesis of  $\alpha,\alpha$ -dialkyl substrates via thiocyanates.

## 2.2.4 Disulfide Approach

A 1996 report from Langlois reported that disulfides could be treated with the Ruppert-Prakash reagent in the presence of TBAF to yield the corresponding trifluoromethyl sulfide.<sup>51</sup> We elected to use cyclohexyl thiol as a test substrate since that exact compound was reported in the paper. Cyclohexanethiol **2.39** was cleanly converted to the corresponding disulfide **2.40** by treatment with pyridine in the presence of I<sub>2</sub> (Scheme 2.9). While the Langlois paper reported the treatment of the disulfide with the Ruppert-Prakash reagent gave a modest 46% yield of the desired product, we isolated only trace amounts of desired product **2.41**.

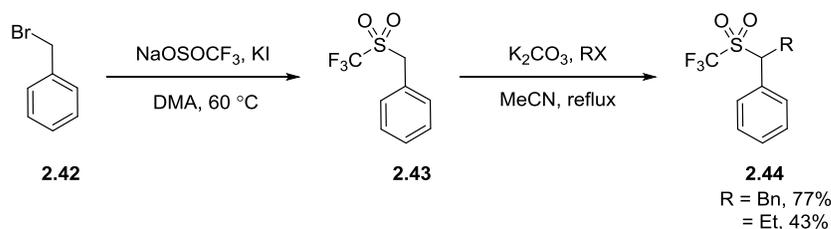


Scheme 2.9. Attempted preparation of alkyl trifluoromethyl sulfides.

A possible explanation for the failure of these reactions appeared in 2013.<sup>52</sup> Once activated by F<sup>-</sup>, the resultant CF<sub>3</sub> anion is quite basic and unstable. There are a number of decomposition pathways, including abstraction of protons from solvent. The secondary disulfide may not be sufficiently electrophilic to trap the CF<sub>3</sub> anion prior to decomposition. The desired product may be forming, but then undergoing elimination to form cyclohexene.

### 2.2.5 Sequential Alkylation & Acylation

Given the challenges that had arisen with all previous approaches, we elected to pursue a sequential alkylation approach. As described in Scheme 2.10, benzyl triflone **2.43** was easily prepared via treatment of benzyl bromide **2.42** with Langlois reagent and potassium iodide in DMA.<sup>30,53</sup> Two secondary alkyl triflones **2.44** were readily prepared from benzyl triflone, in good (R = Bn, 77%) to modest (R = Et, 43%) yield. It was expected that the desired target was now easily achievable.



*Scheme 2.10. Preparation of substituted benzyl triflones.*

Deprotonation of 2° alkyl triflone **2.44** was facile, as evidenced by the dramatic color change observed upon addition of base. Despite exhaustive experimentation, the desired acylated product **2.45** was never observed (Figure 2.7). Either recovered starting material or severe decomposition was observed. The nature of the base was varied (NaH, LDA, *n*-BuLi) in different polar solvents

(THF or DMF) with and without the addition of additives (HMPA or LiCl) intended to increase nucleophilicity of anion. Additionally, the effect of changing the leaving group on the acylating agent was investigated.

Mander was the first to report on the use of cyanoformate reagents to promote C-acylation of ketone enolates to form  $\beta$ -ketoesters.<sup>54</sup> Allyl cyanoformate was prepared according to literature<sup>55</sup> from allyl chloroformate, sodium cyanide and 18-crown-6. Use of the Mander-type reagent in the acylation, however, was unsuccessful. Yet another type of acylating agent was developed by Trost in which imidazole was the leaving group.<sup>56</sup> This reagent was easily prepared from allyl alcohol and 1,1'-carbonyldiimidazole, however it was equally unsuccessful in promoting acylation of triflone anions.

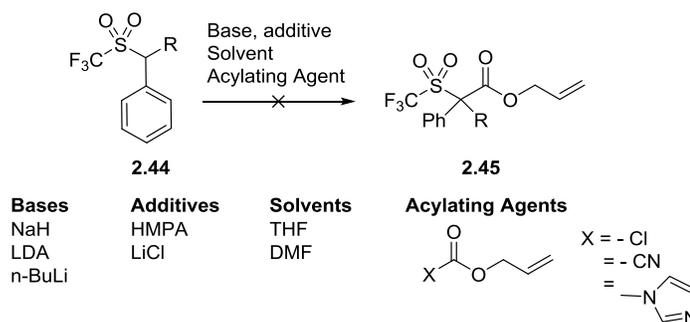


Figure 2.7. Attempts at acylation of secondary benzyl triflates.

## 2.2.6 Insight Into Behavior of $\alpha$ -Triflyl Anions

Careful examination of the physical organic literature associated with  $\alpha$ -sulfonyl anions, and in particular for  $\alpha$ -triflyl anions, gave some insight into these

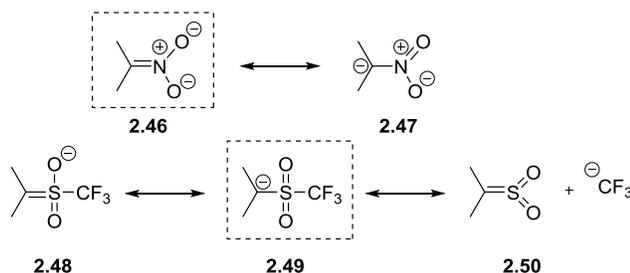


Figure 2.8. Dominant resonance structure for  $\alpha$ -nitro and  $\alpha$ -triflyl carbanions.

results. It is generally accepted that  $\alpha$ -nitro anions are resonance stabilized, and that the structure is best represented by that with a carbon-nitrogen double bond **2.46** (as shown in Figure 2.8). The CF<sub>3</sub>SO<sub>2</sub><sup>-</sup> group is an even stronger electron withdrawing group than the nitro ( $\sigma_p = 0.96$  for CF<sub>3</sub>SO<sub>2</sub>, while  $\sigma_p = 0.81$  for NO<sub>2</sub>), however the mode of stabilization for carbanions has been found to be remarkably different.<sup>57,58</sup> In solution, the stabilization for  $\alpha$ -triflyl anions is proposed to be due to polarization effects, rather than resonance or negative hyperconjugation and best represented by **2.49**.

Remarkable solvent effects have been noted during the study of the basicity and nucleophilicity of benzyl triflones; these solvent effects are completely inverse to that of analogous benzyl nitro compounds.<sup>58</sup> This is illustrated exceptionally well in measurements of relative pK<sub>a</sub> values for benzyltriflone and phenylnitromethane. In 1:1 MeOH:DMSO, benzyltriflone is 7 pK<sub>a</sub> units less than phenylnitromethane. Yet, in pure DMSO, there is a difference of only 2 pK<sub>a</sub> units.

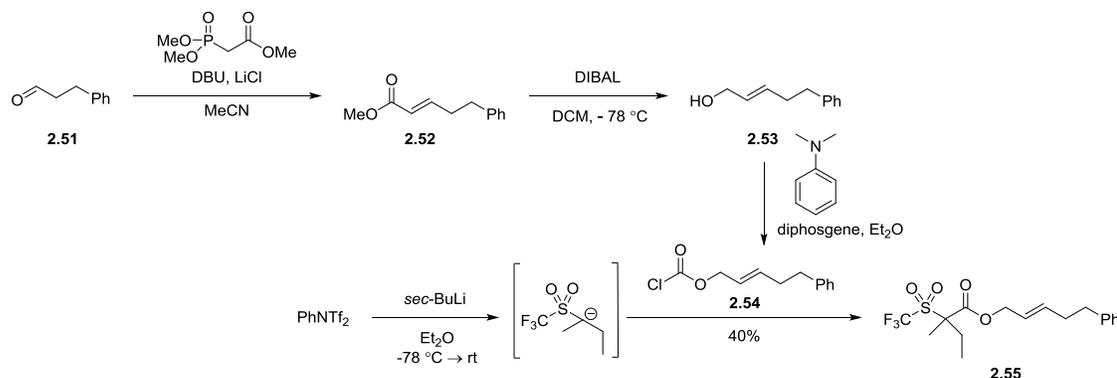
This is presumed to be due to the higher stabilization of polarizable charges in DMSO.<sup>59</sup>

An incredibly detailed theoretical and experimental study that carefully studied chiral  $\alpha$ -triflyl carbanions was published by Gais and co-workers in 2013.<sup>60</sup> Gais has a long-standing interest in  $\alpha$ -triflyl carbanions, having previously established that the lithiated anions are configurationally stable<sup>61</sup> and investigating their potential to induce asymmetry.<sup>62</sup> Ab initio calculations on counter-ion free anions found that  $\alpha$ -triflyl carbanions that were  $\alpha$ -phenyl-substituted were close to planar (i.e., more stable) than those that were alkyl substituted. The anion was more distorted and therefore, more unstable. This provides some explanation why *sec*-butyl triflone anion was successfully acylated, whereas the derivatives of benzyl triflone were not.

## 2.3 Extending Substrate Scope (Allylic ester)

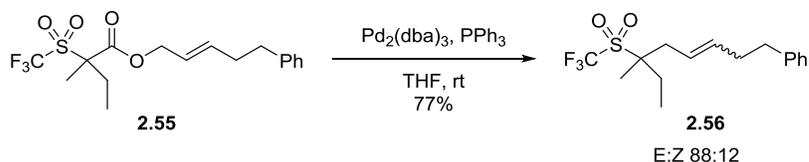
### 2.3.1 Substrate preparation

Although we were ultimately unable to extend the substrate scope with respect to the nature of the dialkyl groups, it was possible to prepare substituted allylic esters. In order to evaluate the feasibility of the proposed desulfonylation of



Scheme 2.11. Synthesis of  $\alpha, \alpha$ -disubstituted substrate with allylic substitution.

the allylated products, we elected to prepare a substrate whose desulfonylated product would be unlikely to be volatile. To this end, allylic alcohol **2.53** was prepared from a Horner-Wadsworth-Emmons olefination of hydrocinnamaldehyde **2.51** with trimethyl phosphonoacetate, followed by DIBAL reduction of ester

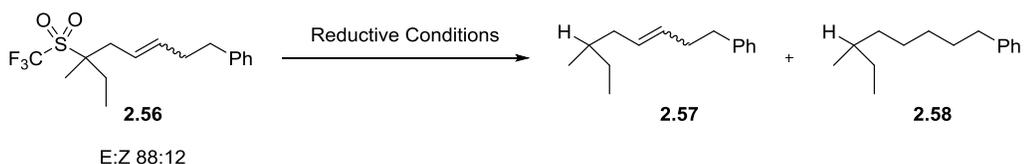


*Scheme 2.12. Pd-catalyzed DcA on allylic substituted substrate.*

**2.52.**<sup>63</sup> The desired chloroformate was prepared via treatment of the allylic alcohol with diphosgene and *N,N*-dimethylaniline in quantitative yield (Scheme 2.11). Compound **2.55** was prepared in analogy to original substrate, albeit in more modest yield. This substrate was subjected to the same palladium-catalyzed decarboxylative allylation conditions (Scheme 2.12) and yielded the expected homoallylic triflone in 77% yield as an 88:12 mixture of E/Z isomers.

### 2.3.2 Reductive Cleavage of Homoallylic Triflone

Conditions for the carbon-sulfur bond cleavage were screened. Treatment with magnesium metal in methanol simply returned starting material. We turned to Raney nickel under a H<sub>2</sub> atmosphere to effect the desired transformation (Scheme 2.13). While we were successful in reducing the carbon-sulfur bond (**2.57**), there was also competitive reduction of the double bond (**2.58**). Careful monitoring of the



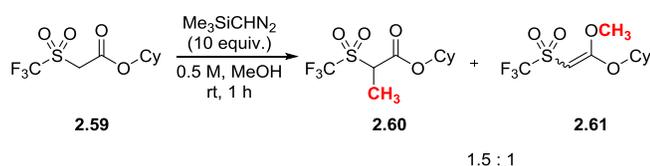
*Scheme 2.13. Reductive cleavage of homoallylic triflone.*

reaction by TLC demonstrated that both reductions were occurring at similar rates, thus making it impossible to obtain the desulfonylated alkene in good yield.

## 2.4 Methylation of $\alpha$ -Triflyl Esters

*Note: The research described in Section 2.4 were initiated by Jennifer Crichton in the Manthorpe research lab as part of a B.Sc. Honours Thesis (2008-2009) and continued by Han Kong, M.Sc. Thesis (2009-2011).*

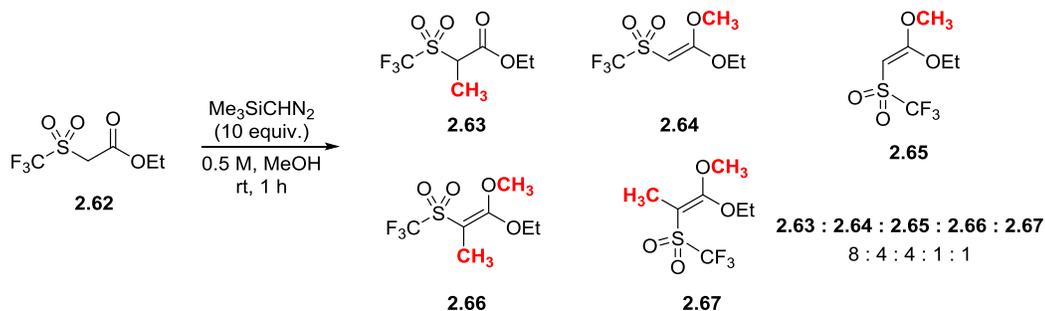
In the course of evaluating the alkylation of  $\alpha$ -triflyl esters, it occurred to us that we might be able to exploit the high acidity of the  $\alpha$  protons for alkylation. The pKa of ethyl trifluoromethanesulfonylacetate is 6.4 in DMSO, while acetic



Scheme 2.14. Initial methylation of  $\alpha$ -triflyl ester.

acid has a pKa of 12.6 in DMSO. We hypothesized that we could alkylate these systems using diazomethane. Two substrates were prepared to evaluate the feasibility of this reaction. Treatment of cyclohexyl triflylacetate with  $\text{TMSCHN}_2$  (which, for safety reasons, was used as a diazomethane synthon) resulted in a 1.5 : 1 ratio of C-methylation (**2.60**) to O-methylation (**2.61**) (mixture of E/Z isomers) (Scheme 2.14).

The second substrate, ethyl triflylacetate, was treated with TMSCHN<sub>2</sub> in an identical fashion, but gave a much more complicated mixture of products (Scheme 2.15). Despite the complex product distribution, this experiment provided proof of



Scheme 2.15. Methylation of  $\alpha$ -triflyl ethyl acetate.

principle that esters could react with TMS diazomethane. We then sought to optimize the reaction conditions to promote selective methylation. Using the amide substrate, the reaction conditions were optimized to 2.5 equivalents of TMS diazomethane in ethanol (1.0 M). Using the optimized conditions, the substrate scope was explored for amides (Table 2.2) and for ketones (Table 2.3).

Table 2.2. Substrate scope for methylation of  $\alpha$ -triflyl amides.

Entry	Substrate	Product	Conv. (%) <sup>a</sup>	Isolated Yield (%)	Z/E ratio <sup>b</sup>
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) <sup>c</sup>	100:0
5			25 (12 h) 45 (60 h)	16 (12 h) 23 (60 h)	100:0
6		No Reaction	0 <sup>d</sup> 0 <sup>e</sup>		

<sup>a</sup> Determined by integration of <sup>1</sup>H NMR signals in spectra of crude mixtures

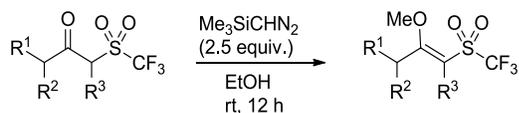
<sup>b</sup> Assigned via 2D NOESY experiment

<sup>c</sup> Crude yield

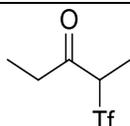
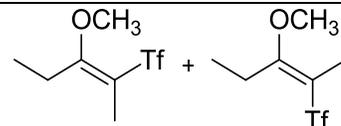
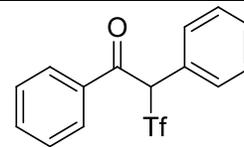
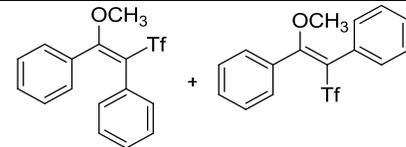
<sup>d</sup> Under standard conditions

<sup>e</sup> 5 equiv. Me<sub>3</sub>SiCHN<sub>2</sub>, 1 M in EtOH, rt, 5 d

Table 2.3. Substrate scope for methylation of  $\alpha$ -triflyl ketones



Entry	Substrate	Product	Conv. (%) <sup>a</sup>	Isolated Yield (%)	Z/E ratio <sup>b</sup>
1			100	66 89 <sup>c</sup>	-
2			100	92	100:0
3			100	68	100:0

4			100	77	25:75
5			82	48	82:18 <sup>d</sup>

<sup>a</sup> Determined by integration of <sup>1</sup>H NMR signals in spectra of crude mixtures

<sup>b</sup> Assigned via 2D NOESY experiment

<sup>c</sup> 10 equiv. Me<sub>3</sub>SiCHN<sub>2</sub>, 1 M in MeOH, rt, 3 h.

<sup>d</sup> Unable to assign isomers

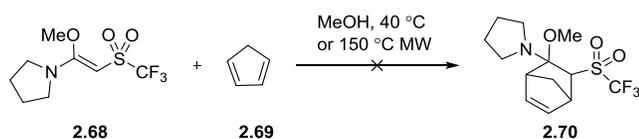
Cyclic amides (entries 1 and 2, Table 2.2) were methylated in good yields, however more sterically demanding amides (entries 3 and 4, Table 2.2) were not nearly as reactive. Longer reaction times were required and isolated yields were substantially lower. The use of a secondary amide (entry 5, Table 2.2) afforded a low yield of methylated product as well. All methylated amides, however, gave exclusively *Z*-alkenes. It was found that  $\alpha$ -methyl amides were completely unreactive under the optimized conditions (entry 6, Table 2.2). The substrate scope for  $\alpha$ -triflyl ketones was also explored. Cyclic (entry 1, Table 2.3) and  $\alpha$ -methylene substrates (entries 2 and 3, Table 2.3) were successfully methylated in good to excellent yield and with exclusive *Z*-alkene formation. Substrates with  $\alpha$ -substitution were reactive, however the selectivity was substantially reduced (entries 4 and 5, Table 2.3).

## 2.5 Attempted Derivatization of Triflyl-Substituted Ambiphilic Alkenes

*Note: The experiments described in Section 2.5 were performed by Han Kong in the Manthorpe research group as part of his M.Sc. thesis (2009-2011)<sup>64</sup>*

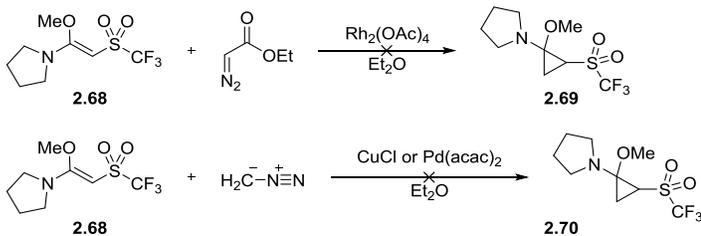
The products of methylation of  $\alpha$ -triflyl carbonyl compounds can be classified as ambiphilic alkenes. The presence of both a strong electron-donating group (-OMe) and a strong electron-withdrawing group (-SO<sub>2</sub>CF<sub>3</sub>) raises interesting questions about the type of reactivity the alkene might exhibit. The next section delineates the attempts made to elaborate these ambiphilic alkenes.

The use of an ambiphilic alkene as a dienophile in a Diels-Alder reaction was explored first (Scheme 2.16). Compound **2.68** was found to be unreactive towards cyclopentadiene at 40 °C in MeOH, as well as at 150 °C via microwave heating.



*Scheme 2.16. Attempted derivatization of ambiphilic alkene via Diels-Alder reaction.*

Efforts were turned towards cyclopropanation of the ambiphilic alkenes. It was anticipated that a new class of donor-acceptor cyclopropanes could be prepared. Treatment of **2.68** with ethyl diazoacetate in the presence of rhodium catalyst resulted in quantitative recovery of the starting material. Likewise, only starting material was recovered when **2.68** was treated with diazomethane in the presence of copper or palladium catalyst (Figure 2.9).



*Figure 2.9. Attempted cyclopropanation of ambiphilic alkenes.*

Efforts were turned away from the use of diazo-based cyclopropanating reagents and focused on the use of the Corey-Chaykovsky reagent (Figure 2.10). Trimethylsulfoxonium iodide was deprotonated with sodium hydride in THF, then combined with ambiphilic alkene **2.68**. Instead of the expected cyclopropane product, we were quite surprised to find that the product was the corresponding  $\alpha$ -triflyl amide **2.69** (75% yield). This unique reactivity is also observed when ambiphilic alkenes derived from ketones (**2.70**) are used. This is rationalized by nucleophilic attack by ylide on the methyl group of the vinyl methyl ether. The resulting electron cascade reforms the carbonyl, thus moving an electron pair onto the  $\alpha$ -carbon. Acidic work-up protonates that position.

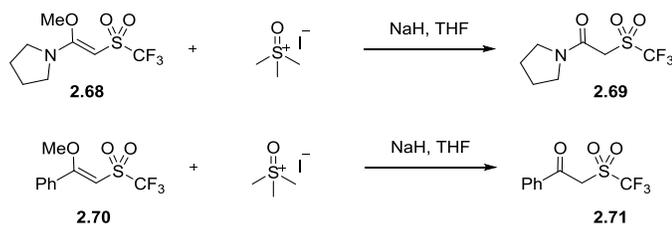


Figure 2.10. Unexpected products from attempted Corey-Chaykovsky cyclopropanation of ambiphilic alkenes.

As a final effort towards doing something useful with the ambiphilic alkenes, **2.68** was treated with a small and strong nucleophile – methyllithium (Figure 2.11). The substrate was largely unreactive but trace amounts of **2.72** were obtained. The formation of this product can be rationalized by deprotonation of the vinylic proton by the basic methyllithium, followed by intermolecular nucleophilic attack of the carbanion on the methyl ether of another molecule of **2.68**. Incredibly, even

simple hydrogenation of **2.68** was not straightforward (Figure 2.11). A small amount of product **2.73** was isolated that showed a net loss of methoxide.

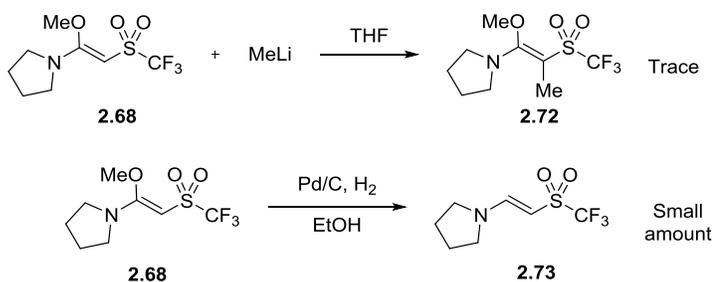
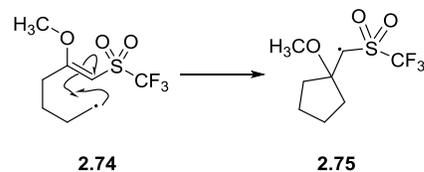


Figure 2.11. Attempted nucleophile addition and hydrogenation of ambiphilic alkenes.

## 2.6 Radical trap work

*Note: The work described in Section 2.6 was by Monica Gill as an extension of the previous experiments performed by Han Kong (Sections 2.4 - 2.5)*

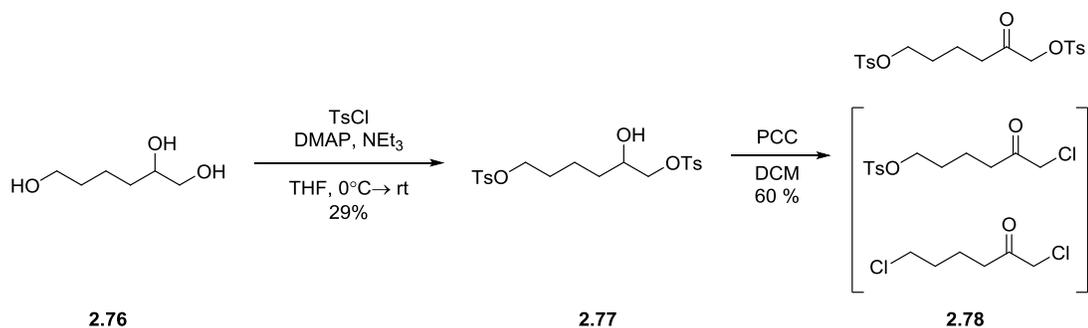
With the inability of the ambiphilic alkenes to be elaborated, we designed a substrate in which an intramolecular radical 5-exo dig ring closure could be envisioned (Scheme 2.17). We sought to employ an ambiphilic alkene with an alkyl chain, terminating with a halogen. Generation of the very reactive primary radical **2.74** would conceivably attack the alkene.



Scheme 2.17. Proposed radical cyclization of ambiphilic alkene derivative.

### 2.6.1 Preparation of appropriate substrate

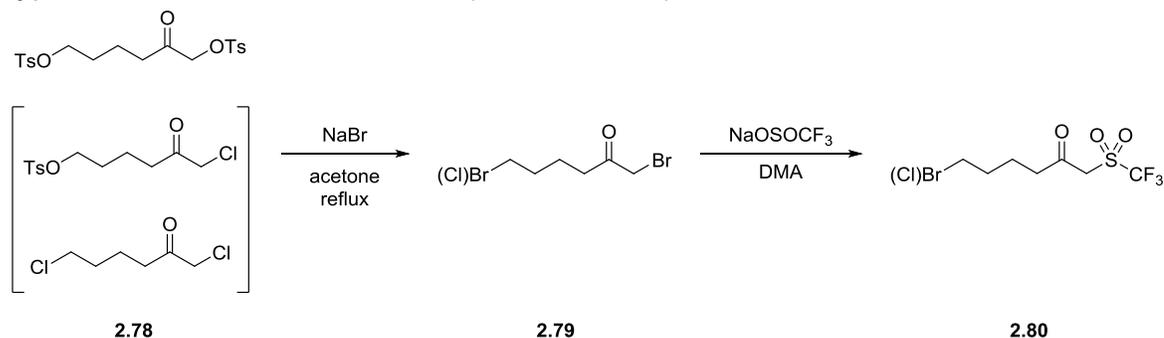
It was envisioned that 1,2,6-hexanetriol **2.76** could serve as a good starting point for the desired substrate (Scheme 2.18). Selective protection of the primary alcohol groups was attempted, adapting a procedure from Lebar and Baker.<sup>65</sup> The



Scheme 2.18. Use of 1,2,6-triolhexane as starting material for cyclization substrate.

low yield for this reaction is attributed to a broad distribution of products including both possible monoprotected compounds, and a large amount of tri-protected product. The low cost of the triol and the reagents offset the poor yield well. Oxidation of secondary alcohol **2.77** to the ketone **2.78** was accomplished using PCC (employing a procedure adapted from Ogawa)<sup>66</sup> was successful, although there was some displacement of both of the tosylates by chloride ion.

This was considered inconsequential as the next step was a Finklestein-type reaction to install bromides (Scheme 2.19). Dibromide **2.79** was isolated, but

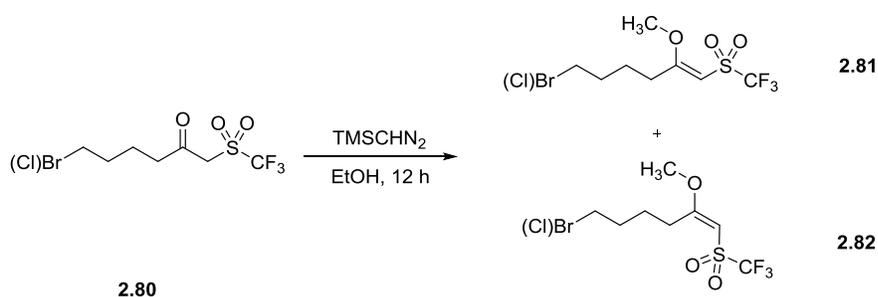


Scheme 2.19. Preparation of  $\alpha$ -triflyl ketone cyclization

still had some chloro substitution in both positions. The triflone group was installed via the standard conditions with sodium triflinate and *N,N*-dimethylacetamide. The crude mixture revealed desired product **2.80**, as well as some bis-triflone compound. Chromatographic separation of these two compounds was exceptionally challenging - none of the standard solvent combinations (hexane/EtOAc or ether, DCM, etc) provided satisfactory separation by TLC. We hypothesized that we might be able to exploit the fact that the desired product had half the number of fluorine atoms than did the impurity. We were pleased to see that the use of  $\alpha,\alpha,\alpha$ -trifluorotoluene allowed us to differentiate between these two compounds.

### 2.6.2 Attempts at radical and anionic cyclization of ambiphilic alkene

The  $\alpha$ -triflyl ketone **2.80** was then treated with TMSCHN<sub>2</sub> in EtOH to give a mixture of (*E*) and (*Z*) ambiphilic alkenes (Scheme 2.20). These were separated via flash chromatography and the alkene geometry was assigned using NOESY.



Scheme 2.20. Methylation of  $\alpha$ -triflyl ketone cyclization substrate.

Each of these compounds was treated separately under conditions that could potentially effect a cyclization (Figure 2.12). The first substrate, **2.81**, was treated with tributyltin hydride in the presence of AIBN to generate the requisite primary

radical. Unfortunately, no cyclization was observed. The main product was a terminal methyl group, presumably the result of radical termination. The second isomer, **2.82**, was treated with *t*-BuLi, in an attempt to effect a lithium-halogen exchange and then cause a cyclization via intramolecular nucleophilic attack on the ambiphilic alkene. Unfortunately, the major product was simply the protonated version. No desired cyclized product was observed.

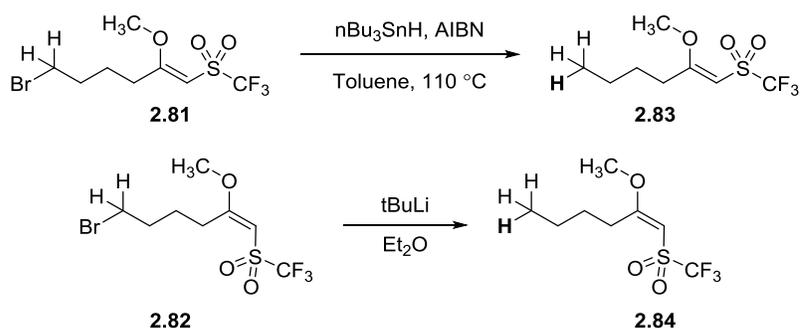
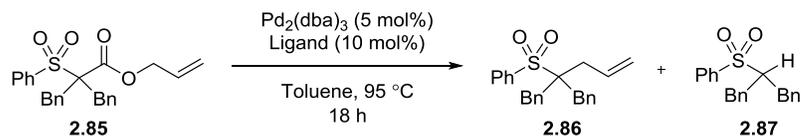


Figure 2.12. Attempted radical (top) and anionic (bottom) cyclization of ambiphilic alkene derivatives.

## 2.7 Contemporary Work

In the course of our work on elaborating the substrate scope for  $\alpha,\alpha$ -dialkylated  $\alpha$ -triflyl allyl acetates, Tunge and Weaver reported on a Pd-catalyzed DcA of phenyl sulfones.<sup>67</sup> Figure 2.13 illustrates the optimization that was required



Entry	Ligand	<b>2.86</b> : <b>2.87</b>
1	$\text{PPh}_3$	1:1
2	dppp	3.5:1
3	dppb	3.1:1
4	dppf	3.5:1
5	Josiphos	4.5:1
6	BINAP	11.3:1
7	Amino-BINAP	No rxn

Figure 2.13. Tunge's optimization of Pd-cat DcA for phenyl sulfones.

to minimize the formation of the protonated byproduct **2.87**. Notably, the reaction temperature for  $\alpha,\alpha$ -dialkyl phenyl sulfones was substantially higher and much longer reaction times than for our triflone substrate. When  $\text{PPh}_3$  was used as ligand, a poor product distribution was obtained. In evaluating the substrate scope, they noted a dramatic rate enhancement when a chloro or phenyl substituent was one of the  $\alpha$ -substituents. The reaction proceeded in 3-4 hours for  $\alpha$ -chloro substrates at 95 °C, while substrates with  $\alpha$ -phenyl substituents reacted at room temperature in 30 minutes. This rate acceleration was attributed to benzylic stabilization of the intermediate anion. The use of the homoallylic sulfones as alkane synthons was also addressed. This report concluded with the reductive cleavage of the C-S bond using Mg in MeOH.

We chose to continue our investigation into Pd-catalyzed DcA reactions of electron-deficient sulfones despite the Tunge report. The remarkable reactivity of the triflones, the complete inhibition of protonated product, and the exceptionally mild reaction conditions made this a valuable class of substrates to investigate. The issue of elaboration of substrate scope persisted, however. This is addressed fully in Chapter 3.

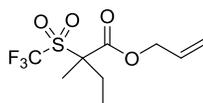
## 2.8 Experimental

### General

All reagents were purchased from commercial sources and were used as received, without further purification, unless otherwise noted. DCM, toluene, Et<sub>2</sub>O, were distilled from CaH<sub>2</sub> immediately prior to use. Tetrahydrofuran was distilled from lithium aluminum hydride or sodium/benzophenone prior to use. Reactions were monitored by thin-layer chromatography (TLC) using glass-backed extra hard layer (60 Å) TLC plates from Silicycle and visualized by fluorescence quenching under ultraviolet (UV) light and/or staining using potassium permanganate or ceric ammonium nitrate. 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 Still *et al.*<sup>68</sup> or by automated chromatography on a Biotage Isolera One equipped with a UV detector. Concentration in vacuo refers to rotary evaporation with a 40 °C water bath at the appropriate pressure for the given solvent. Yields refer to purified and spectroscopically pure compounds unless indicated as crude. NMR spectra were recorded on a Bruker Avance III 300 or Bruker AMX 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm). Spectra are referenced to the internal standard tetramethylsilane (TMS) (0.00 ppm). <sup>19</sup>F NMR spectra are referenced to trifluorotoluene (- 63.7 ppm). Infrared (IR) spectra were recorded on a Varian 1000 Scimitar Series or an ABB Bomem MB series spectrometer. Absorptions are given in wavenumbers (cm<sup>-1</sup>). High resolution mass spectrometry (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV at the Ottawa-Carleton Mass

Spectrometry Center or on a Bruker Maxis Impact Quadrupole-Time of Flight Mass Spectrometer in positive ESI mode at the McGill Chemistry Mass Spectrometry Center.

**Allyl 2-methyl-2-((trifluoromethyl)sulfonyl)butanoate (2.17)**



An oven-dried Schlenk flask was charged with *N*-phenyl-bis(trifluoromethanesulfonimide) (500 mg, 1.4 mmol, 1.0 equiv.) and was flushed with argon. THF (7 mL, 0.2 M) was added via syringe. The solution was cooled to -78 °C and *sec*-butyllithium (1.4 M in cyclohexane, 2.5 mL, 3.5 mmol, 2.5 equiv.) was added dropwise. The reaction mixture was allowed to warm over one hour, and was then cooled to -78 °C. Allyl chloroformate (0.140 mL, 1.3 mmol, 0.95 equiv) was added dropwise. The reaction mixture was stirred for 8 hours, warming to room temperature slowly as the cooling bath evaporated. The reaction was quenched with saturated (NH<sub>4</sub>)<sub>2</sub>SO<sub>4(aq)</sub>. Mixture was extracted with 2 x 10 mL Et<sub>2</sub>O, and the combined organic extracts were washed with brine and then dried over MgSO<sub>4</sub>. Filtration, followed by concentration in vacuo, yielded a pale yellow oil. Purification via flash chromatography (2% EtOAc/hexane) gave a colorless oil (194 mg, 51%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 5.92 (ddt, *J* = 17.1, 10.3, 6.0 Hz, 1H), 5.42 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.32 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.73 (m, 2H), 2.50 (dq, *J* = 13.6, 7.6 Hz, 1H), 2.04 (dq, *J* = 13.6, 7.6 Hz, 1H), 1.74 (s, 3H), 1.01 (t, *J* = 7.6 Hz, 3H).

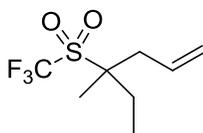
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 165.5, 130.5, 120.4 (q, *J* = 329 Hz), 120.1, 74.7, 67.6, 25.9, 6.0, 8.3.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, 376.5 MHz): -70.9.

**IR** (thin film): 3092, 2987, 2952, 2918, 2890, 2849, 1745, 1462, 1363, 1316, 1203, 1156, 1128, 1097, 1052.

**HRMS**: molecular ion (C<sub>9</sub>H<sub>13</sub>F<sub>3</sub>O<sub>4</sub>S<sup>+</sup>) not detected. *m/z* calcd for C<sub>6</sub>H<sub>8</sub>F<sub>3</sub>O<sub>3</sub>S<sup>+</sup>: 217.0135; Found: 217.0121 (2.2% intensity). *m/z* calcd for C<sub>8</sub>H<sub>13</sub>O<sub>2</sub><sup>+</sup>: 141.0910; Found: 141.0915 (4.0 % intensity).

#### **4-Methyl-4-((trifluoromethyl)sulfonyl)hex-1-ene (2.18)**



A 15 mL round bottom flask was flame dried under vacuum and backfilled with argon. The flask was charged with Pd<sub>2</sub>(dba)<sub>3</sub> (5.8 mg, 0.0063 mmol, 0.025 equiv) then sealed with a septum and flushed with argon. THF (2.5 mL, 0.1 M) was added via syringe and triphenylphosphine (6.6 mg, 0.025 mmol, 0.1 equiv) was added in one portion, then flask was flushed with argon. The catalyst was allowed to form for 30 minutes at room temperature. The substrate (68.0 mg, 0.25 mmol, 1.0 equiv) was dissolved in a minimum of dry THF (200 μL) and this solution was added dropwise to the catalyst solution. The reaction was monitored by TLC and was complete in less than 30 minutes. The solvent was removed in vacuo, then the crude mixture was purified via flash chromatography (2.5% EtOAc/hexane) to give a colorless oil (53 mg, 92%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): 5.80 (ddt, *J* = 16.8, 10.0, 7.6 Hz, 1H), 5.22 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.24 – 5.26 (m, 1H), 2.76 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.57 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.03 (dq, *J* = 14.8, 6.8 Hz, 1H), 1.88 (dq, *J* = 14.8, 7.2 Hz, 1H), 1.48 (d, *J* = 1.2 Hz, 3H), 1.09 (t, *J* = 7.6 Hz, 3H).

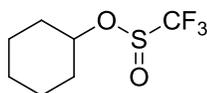
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 75 MHz): 129.5, 120.9, 120.7 (q, *J* = 332 Hz), 56.2, 37.4, 26.7, 19.2, 8.2.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, 376.5 MHz): -71.1.

**IR** (thin film): 1622, 1594, 1439, 1419, 1341, 1204, 1121, 948, 887.

**HRMS**: molecular ion not observed. *m/z* calc'd for C<sub>7</sub>H<sub>13</sub><sup>+</sup>: 97.1012; Found: 97.1039 (31.7% intensity).

### Cyclohexyltrifluoromethylsulfinate (2.31)



An oven-dried round bottom flask was charged with mesitylenesulfonyl chloride (3.32 g, 15.2 mmol, 1.0 equiv) and sodium trifluoromethylsulfinate (2.50 g, 16.0 mmol, 1.05 equiv). Under argon atmosphere, acetonitrile (20 mL, 0.8 M with respect to sodium trifluoromethylsulfinate) was added. The reaction mixture was stirred at room temperature for 1 hour, then cooled in an ice bath. A solution containing cyclohexanol (1.61 mL, 15.2 mmol, 1.0 equiv), pyridine (1.23 mL, 15.2 mmol, 1.0 equiv) and acetonitrile (7.0 mL, 2.2 M) was prepared and added dropwise over 5 minutes to the cooled solution prepared previously. The reaction mixture was allowed to warm slowly to room temperature over 18 hours. The milky

reaction mixture was then diluted with Et<sub>2</sub>O (100 mL) and washed with water (5 x 50 mL). The organic phase was washed with 3 x 50 mL brine, then dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo to produce a yellow oil (2.30g, 70%). This product was used without further purification in the next step. A sample was purified for characterization using flash chromatography (5-10% diethyl ether/hexane). The compound was isolated as a colorless, volatile liquid.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 4.54 (m, 1H), 1.19 – 2.02 (m, 10H).

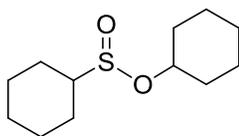
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 75 MHz): δ 122.7 (q, *J* = 334 Hz), 82.0, 33.1, 33.0, 24.8, 23.5, 23.4.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, 376.5 MHz): δ -144.5

**IR** (thin film): 2942, 2864, 1732, 1453, 1373, 1200, 1132, 1033, 1004.

**HRMS**: molecular ion not observed. *m/z* calc'd for C<sub>6</sub>H<sub>11</sub>SO<sub>2</sub><sup>+</sup>: 147.0474. Found: 147.0498 (1.2 % intensity). *m/z* calc'd for CF<sub>3</sub>SO<sup>+</sup>: 116.9622. Found: 116.9594 (0.9% intensity). *m/z* calc'd for C<sub>6</sub>H<sub>11</sub><sup>+</sup>: 83.0855. Found: 83.0877 (100% intensity).

### **Cyclohexyl cyclohexanesulfinate (2.32)**



Cyclohexyl trifluoromethylsulfinate (505 mg, 2.3 mmol, 1.0 equiv) was dissolved in toluene (12.5 mL, 0.2M) and the solution was cooled to 0 °C. Cyclohexylmagnesium chloride (2.9 mL, 2.0 M in diethyl ether, 5.8 mmol, 2.5 equivs) was added dropwise over 5 minutes. Cooling bath was maintained for 15 minutes, then reaction mixture was allowed to warm to room temperature over 45

minutes. The reaction was quenched with sat.  $\text{NH}_4\text{Cl}_{(\text{aq})}$  and extracted with 3 x 25 mL DCM. The combined organic extracts were washed with brine (3 x 25 mL), then dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated in vacuo. The crude product was purified via flash chromatography (10% EtOAc/hexane) to yield 213 mg (40%).

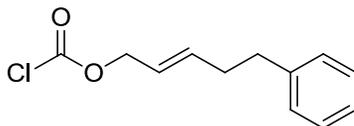
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.81 (tt,  $J = 9.6, 4.0$  Hz, 1H), 2.52 (tt,  $J = 11.2, 4.0$  Hz, 1H), 1.68-2.01 (m, 10H), 1.21 – 1.61 (m, 12H).

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  78.8, 63.8, 33.8, 32.9, 25.7, 25.22, 25.2, 25.1, 24.5, 23.8, 23.7 (broad peak with unresolved shoulder).

**IR** (thin film): 2933, 2856, 1451, 1370, 1134, 1035, 1012.

**HRMS**:  $m/z$  calcd for  $\text{C}_{12}\text{H}_{22}\text{O}_2\text{S}$ : 230.1341; Found: 230.1326.

#### 5-phenylpent-2-en-1-yl chloroformate (2.54)



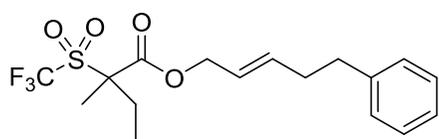
5-phenylpent-2-en-1-ol (prepared according to Kobayashi, *et al.*<sup>63</sup>) (600 mg, 3.7 mmol, 1.0 equiv) was dissolved in  $\text{Et}_2\text{O}$  (3.7 mL, 1.0 M relative to allylic alcohol). This solution was cooled to 0 °C, then diphosgene (265  $\mu\text{L}$ , 2.2 mmol, 0.6 equiv) was added dropwise to solution. Following 5 minutes of stirring, *N,N'*-dimethylaniline (470  $\mu\text{L}$ , 3.7 mmol, 1.0 equiv) was added dropwise. The temperature was maintained at 0°C for 20 minutes after addition of base, then the reaction mixture was allowed to warm to room temperature. After 8 hours, argon was bubbled through the reaction mixture to remove any remaining phosgene. This mixture was then diluted with  $\text{Et}_2\text{O}$  and filtered through a medium porosity fritted

funnel. The filtrate was concentrated in vacuo to give desired product (quantitative yield). The product was used without any further purification.

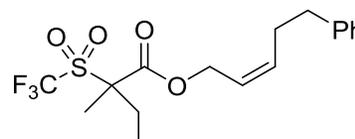
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.30 – 7.33 (m, 2H), 7.18 – 7.24 (m, 3H), 5.92 – 6.01 (m, 1H), 5.61 – 5.70 (m, 1H), 4.60 (d, *J* = 6.8 Hz, 2H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.44 (dt, *J* = 7.6, 7.2 Hz, 2H)

**5-Phenylpent-2-en-1-yl-2-methyl-2-((trifluoromethyl)sulfonyl)butanoate**

**(2.55)**



Major



Minor

An oven-dried Schlenk flask was charged with *N*-phenyl-bis(trifluoromethanesulfonimide) (500 mg, 1.4 mmol, 1.0 equiv.) and was flushed with argon. THF (7.0 mL, 0.2 M) was added via syringe. The solution was cooled to -78 °C, then *sec*-butyllithium (1.4 M in cyclohexane, 2.5 mL, 3.5 mmol, 2.5 equiv.) was added dropwise. The reaction mixture was allowed to warm over one hour as the cooling bath evaporated, and was then re-cooled to -78 °C. The previously synthesized allylic chloroformate (292 mg, 1.3 mmol, 0.95 equiv) was added dropwise. The reaction mixture was stirred for 12 hours, while warming to room temperature slowly as cooling bath evaporated. The reaction was quenched with saturated (NH<sub>4</sub>)<sub>2</sub>SO<sub>4(aq)</sub>. The mixture was extracted with 2 x 25 mL Et<sub>2</sub>O, and the combined organic extracts were washed with brine and then dried over MgSO<sub>4</sub>.

Filtration, followed by concentration in vacuo yielded a pale yellow oil. Purification via flash chromatography (10% EtOAc/hexane) gave a colorless oil (214 mg, 40%).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.26 – 7.31 (m, 2H), 7.16 – 7.21 (m, 3H), 5.88 (m, 1H), 5.60 (m, 1H), 4.64 (m, 2H), 4.59 (d, minor isomer), 2.71 (t, *J* = 7.2 Hz, 2H), 2.47 (m, unresolved due to overlap with q at 2.40), 2.40 (q, *J* = 7.6 Hz, 2H), 2.02 (dq, *J* = 15.2, 6.8 Hz, 1H), 1.72 (s, 3H), 0.98 (t, *J* = 7.2 Hz, 3H).

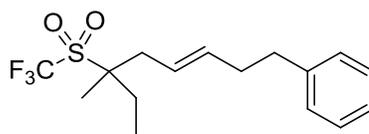
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz) (major isomer): 165.5, 141.3, 137.3, 128.4, 126.0, 124.0, 122.9, 120.4 (q, *J* = 330 Hz), 74.7, 67.7, 35.2, 33.9, 25.9, 16.0, 8.3.

**<sup>19</sup>F NMR** (CDCl<sub>3</sub>, 376.5 MHz): -70.9.

**IR** (thin film): 3029, 2944, 2858, 1742, 1673, 1604, 1497, 1456, 1362, 1316, 1202, 1155, 1127, 1096, 1052, 1030.

**HRMS**: molecular ion not detected. *m/z* calcd for C<sub>5</sub>H<sub>8</sub>F<sub>3</sub>O<sub>2</sub>S<sup>+</sup>: 189.0175; Found: 189.0192 (1.6 % intensity). *m/z* calcd for C<sub>11</sub>H<sub>13</sub><sup>+</sup>: 145.1012; Found: 145.1026 (9.4 % intensity).

**(6-methyl-6-((trifluoromethyl)sulfonyl)oct-3-en-1-yl)benzene (2.56)**



A 15 mL round bottom flask was flame dried and backfilled with argon. The flask was charged with Pd<sub>2</sub>(dba)<sub>3</sub> (6.0 mg, 0.0065 mmol, 0.025 equiv) then sealed with a septum and flushed with argon. THF (2.6 mL, 0.1 M) was added via syringe and Triphenylphosphine (6.8 mg, 0.026 mmol, 0.1 equiv) was added in one portion, then the flask was flushed with argon. The catalyst was allowed to form for 30

minutes at room temperature. The substrate (99.8 mg, 0.26 mmol, 1.0 equiv) was dissolved in a minimum of dry THF (200  $\mu$ L) and this solution was added dropwise to the catalyst solution. The reaction was monitored by TLC and was complete in 2 hours. The solvent was removed in vacuo, then the crude mixture was purified via flash chromatography (2.5% EtOAc/hexane) to give 61 mg (70%).

**$^1\text{H}$  NMR** ( $\text{CDCl}_3$ , 400 MHz): 7.15 – 7.30 (m, 5H), 5.57 – 5.71 (m, 1H, mixture of cis/trans isomers), 5.32 – 5.43 (m, 1H, mixture of cis/trans isomers), 2.71 (t,  $J$  = 7.2 Hz, 2H), 2.60 – 2.67 (m, 1H, mixture of cis/trans isomers), 2.44 - 2.52 (m, 1H, mixture of cis/trans isomers), 2.39 (td,  $J$  = 7.2, 7.2 Hz, 2H), 1.81 – 1.98 (m, 1H, mixture of cis/trans isomers), 1.69 – 1.79 (m, 1H, mixture of cis/trans isomers), 1.40 (d,  $J$  = 0.8 Hz, minor isomer), 1.35 (d,  $J$  = 1.2 Hz, 3H), 1.03 (t,  $J$  = 7.2 Hz, minor isomer, overlapping with peak for major isomer at 1.02 ppm), 1.02 (t,  $J$  = 7.6 Hz, 3H).

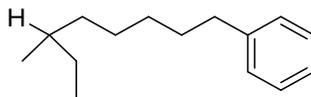
**$^{13}\text{C}$  NMR** ( $\text{CDCl}_3$ , 75 MHz): 141.4, 136.1, 134.1, 128.5 (minor isomer), 128.5, 128.4 (minor isomer), 128.3, 126.0 (minor isomer), 125.9, 122.4, 122.3 (minor isomer), 120.2 (q,  $J$  = 246 Hz), 70.1 (minor isomer), 69.9, 36.1, 35.5 (minor isomer), 35.4, 34.1, 30.4 (minor isomer), 29.4, 26.8 (minor isomer), 26.6, 19.0, 18.9 (minor isomer), 8.4 (minor isomer), 8.3.

**$^{19}\text{F}$  NMR** ( $\text{CDCl}_3$ , 376.5 MHz): -71.1 (minor isomer), -71.2 (major isomer). Ratio of major isomer to minor isomer is 7.3:1 (determined from  $^{19}\text{F}$  NMR integration).

**IR** (thin film): 3028, 2985, 2945, 2857, 1604, 1497, 1456, 1349, 1199, 1138, 1123, 1103, 1030, 974.

**HRMS**:  $m/z$  calcd for  $\text{C}_{16}\text{H}_{21}\text{F}_3\text{O}_2\text{S}$ : 334.1214; Found: 334.1218.

**(5-Methylheptyl)benzene (2.58)**



Raney<sup>®</sup> 2800 nickel, slurry in water, was washed with distilled water five times until the pH of the supernatant was neutral, then the Raney Ni was slurried in anhydrous ethanol. Compound **2.56** (51.7 mg, 0.15 mmol, 1 equiv) was dissolved in anhydrous ethanol in a Schlenk flask, then the washed slurry of Raney Ni was transferred to the flask. The flask headspace was briefly evacuated under vacuum, then backfilled with a balloon of H<sub>2</sub>. This was repeated three times. The reaction flask was left under H<sub>2</sub> pressure at room temperature for 8 hours while monitoring by TLC. The mixture was filtered through Celite, then concentrated *in vacuo* to yield a light yellow oil. Flash chromatography (100% hexane) gave a colorless oil, which was determined to be the desulfonated *and* hydrogenated product.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.25 – 7.29 (m, 2H), 7.15 – 7.19 (m, 3H), 2.60 (t, J = 8.0 Hz, 2H), 1.58 – 1.65 (m, 2H), 1.24 – 1.37 (m, 7H), 1.07 – 1.17 (m, 2H), 0.83 – 0.87 (m, 6H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 143.0, 128.4, 128.2, 125.5, 36.5, 36.0, 34.4, 31.6, 29.7, 29.5, 27.0, 19.2, 11.4.

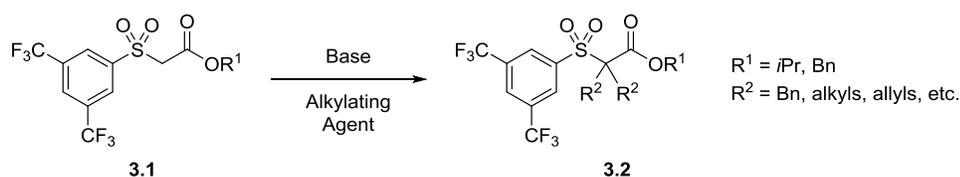
**IR** (thin film): 3433 (br), 3027, 2856, 2928, 2960, 1605, 1496, 1463, 1377, 1030.

**HRMS**: m/z calcd for C<sub>15</sub>H<sub>24</sub>: 204.1878; Found: 204.1869.

## Chapter 3 : Pd-Catalyzed Decarboxylative Allylation of BTMP Sulfones

### 3.1 Alternate Electron-Withdrawing Group

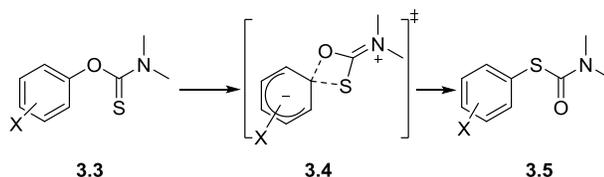
The synthetic challenges associated with the general synthetic approach to triflones led us to investigate other potential sulfones that would facilitate synthesis of a wide variety of substrates, while maintaining the high degree of electron-deficiency needed to facilitate facile decarboxylative allylation. Nájera and co-workers have reported the development of 3,5-bis(trifluoromethyl)phenyl (BTMP) sulfones as alternatives to triflones. They note that the propensity for triflones to extrude SO<sub>2</sub> in a decomposition fashion is problematic.<sup>69,70</sup> A series of  $\pi$ -deficient ( $\alpha$ -arylsulfonyl)acetates, including BTMP sulfones, were prepared (Scheme 3.1). Both isopropyl and benzyl esters were prepared from the reaction of arylthiolates on alkyl bromoacetates, followed by sulfide oxidation by Oxone. In sharp contrast to the analogous triflones, these are easily alkylated under mild conditions form a quaternary center in the  $\alpha$  position. The BTMP sulfones seemed ideal for our purposes.



Scheme 3.1. Nájera's synthesis of  $\alpha,\alpha$ -dialkylated BTMP sulfone esters.

### 3.2 Synthetic Approach

The most often used synthetic route for accessing thiophenols is a thermally induced rearrangement of *O*-arylthiocarbamates (**3.3**), prepared from the corresponding phenol.<sup>71–73</sup> This reaction is commonly known as the Newman-

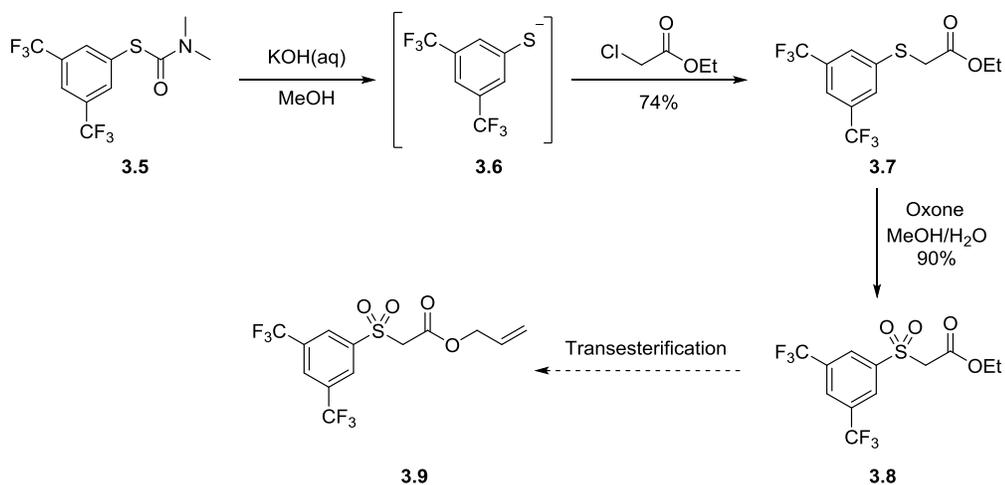


*Scheme 3.2. Mechanism for Newman-Kwart rearrangement.*

Kwart rearrangement and has been shown to proceed via a unimolecular, four-membered 1,3-oxathietane transition state **3.4** (Scheme 3.2).<sup>74</sup> The synthesis began with conversion of the commercially available 3,5-bis(trifluoromethyl)phenol to the *O*-thiocarbamate using *N,N*-dimethylthiocarbamoyl chloride under basic conditions. The corresponding *S*-thiocarbamate **3.5** was obtained through a Newman-Kwart rearrangement performed neat, at 200 °C for 6 hours in 86% yield.<sup>75</sup> This reaction may be conveniently monitored by <sup>1</sup>H NMR, as the peaks arising from the dimethylamino group of the product are very well separated from those of the starting material.

Although it is possible to hydrolyze the *S*-thiocarbamate **3.5** to the corresponding thiol, it was found to be more convenient to perform a one-pot procedure in which the thiolate was intercepted by ethyl chloroacetate (Scheme 3.3). The electrophile was added to the reaction mixture after TLC confirmation that the hydrolysis was complete. The  $\alpha$ -thio ethyl ester **3.7** was isolated in good yield after flash chromatography. Sulfone **3.8** was isolated in excellent yield upon

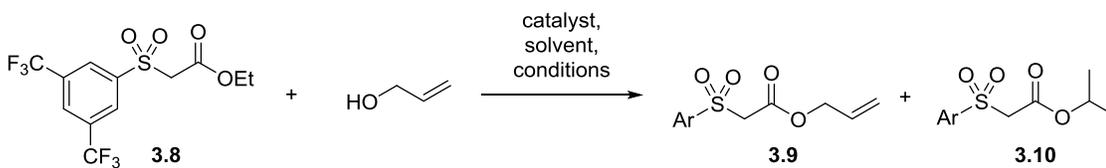
treatment of the sulfide with Oxone (a triple salt with the formula  $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ ).<sup>70</sup>



Scheme 3.3. Synthetic route towards  $\alpha$ -BTMP sulfonyl allyl esters.

It was initially envisioned that sulfone **3.8** would act as a common intermediate for the synthesis of a library of substrates. Transesterification with an appropriate allylic alcohol, followed by alkylation appeared to be the most straightforward approach. Titanium (IV) isopropoxide is a well-known, mild catalyst for transesterification and as such, our investigations began with that reagent.<sup>76</sup>

Table 3.1. Attempted transesterification with  $\alpha$ -BTMP sulfone ethyl ester.



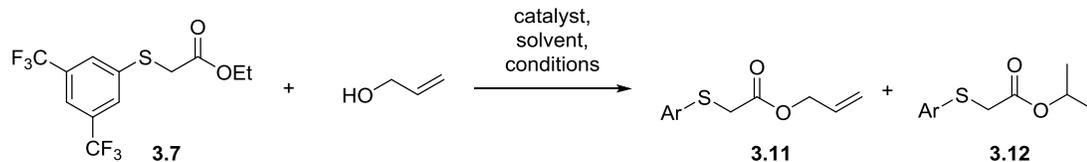
Entry	Equiv ROH	Catalyst	Solvent	Temp (°C)	Time	Et:Allyl:iPr
1	5	Ti(O <i>i</i> Pr) <sub>4</sub>	DCM	40	18 h	14:55:31
2	10	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	65	21 h	0:0:100
3	5	Ti(O <i>i</i> Pr) <sub>4</sub>	PhMe	110	21 h	17:7:75
4	10	Ti(O <i>i</i> Pr) <sub>4</sub>	PhMe	110	21 h	11:5:84
5	5	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	150 ( $\mu$ W)	10 min	12:60:28
6	5	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	150 ( $\mu$ W)	20 min	15:59:26
7	5	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	170 ( $\mu$ W)	10 min	Decomp
8	5	B(OH) <sub>3</sub>	PhMe	110	5 h	100:0:0

Table 3.1 summarizes the attempts at transforming the **3.8** to the corresponding allylic ester **3.9**. Disappointingly, the reaction of the **3.8** with  $\text{Ti}(\text{OiPr})_4$  and allyl alcohol consistently gave a mixture of desired allyl ester **3.9**, starting material **3.8** and byproduct isopropyl ester **3.10** (presumably from transesterification from the titanate reagent). This would not be a critical issue if it were not so challenging to separate very similar molecules (i.e. ethyl ester versus allyl ester versus isopropyl ester). A solvent screen was performed with THF,  $\text{Et}_2\text{O}$ , DCM and toluene. The reaction was relatively insensitive to changes in solvent, and increasing the number of equivalents of allyl alcohol was inconsequential.

Attempts at promoting further conversion and selectivity using microwave heating gave similar results, or when pushed for longer, resulted in an unidentified by-product and apparent decomposition. While never proved conclusively, careful analysis of the crude  $^1\text{H}$  NMR suggested that the unidentified by-product contained an allyl group on the aromatic ring. There was a report of transesterification of ethyl acetoacetate to allyl acetoacetate using boric acid as a catalyst.<sup>77</sup> When this reaction was attempted on **3.8**, only starting material was recovered. This method was not explored any further.

The analogous transesterification on the sulfide ethyl ester **3.7** was evaluated as well (Table 3.2). The results were quite similar to attempted

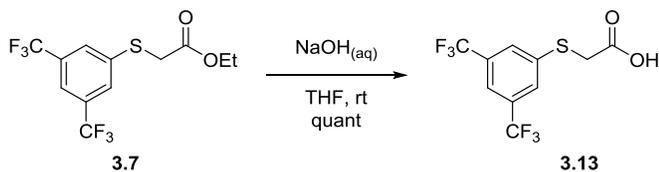
Table 3.2. Attempted transesterification with  $\alpha$ -BTMP sulfide ethyl ester.



Entry	Equiv ROH	Catalyst	Solvent	Temp (°C)	Time	Et:Allyl:Pr
1	5	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	65	18 h	8:71:21
2	10	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	65	18 h	7:67:26
3	5	Ti(O <i>i</i> Pr) <sub>4</sub>	PhMe	110	18 h	17:0:83
4	10	Ti(O <i>i</i> Pr) <sub>4</sub>	PhMe	110	21 h	14:3:83
5	5	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	150 ( $\mu$ W)	10 min	20:59:21
6	5	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	150 ( $\mu$ W)	20 min	19:53:28
7	5	Ti(O <i>i</i> Pr) <sub>4</sub>	THF	170 ( $\mu$ W)	10 min	17:54:29

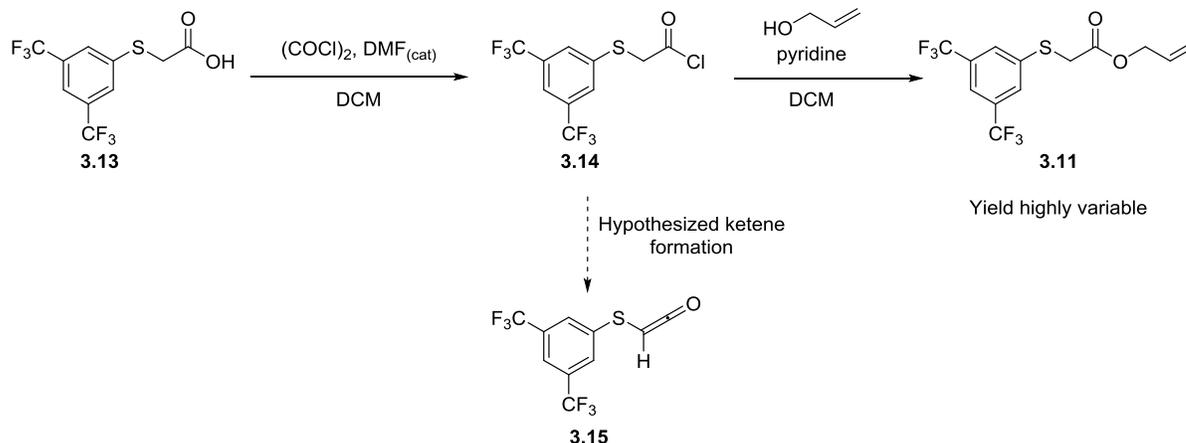
transesterification on sulfone **3.8**. Microwave heating at higher temperatures for shorter periods of time did not improve the product distribution. This method of transesterification was ultimately abandoned.

In Seebach's original report for the use of titanium isopropoxide for transesterification,<sup>76</sup> there is reference made to the fact that the formation of allyl esters via this methodology is challenging due to the relative instability of allyl esters. This instability, i.e. propensity to undergo transesterification with almost any nucleophile, became a recurring theme during the optimization of substrate synthesis.



Scheme 3.4. Saponification of  $\alpha$ -BTMP sulfone ethyl ester.

Attention was turned to ester preparation via carboxylic acid activation methods. Compound **3.7** was cleanly saponified with aqueous NaOH in THF to give virtually quantitative yield of **3.13** with high purity (Scheme 3.4). This carboxylic acid is a bench stable, waxy solid that would end up serving as a branch point for all remaining substrate preparation. Our first attempt involved conversion



*Scheme 3.5. Attempted esterification via acyl chloride.*

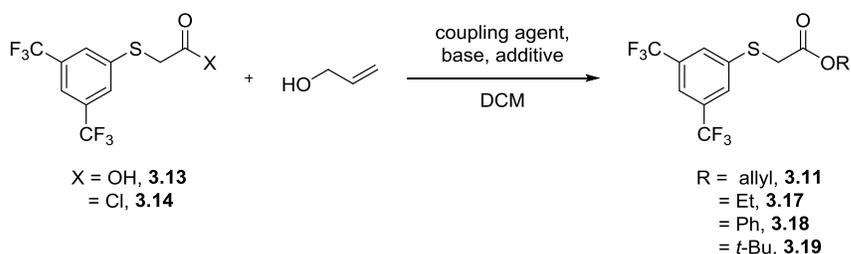
of carboxylic acid **3.13** to acyl chloride **3.14** using oxalyl chloride with catalytic DMF in DCM (Scheme 3.5). The isolation of the acyl chloride was successful, however the subsequent reaction with allyl alcohol and pyridine in DCM gave low and variable yields (Table 3.3) (entry 1). The addition of catalytic DMAP (entry 2) to the reaction conditions improved the yield marginally, but the reaction was unpredictable. It was hypothesized that treatment of the acyl chloride with pyridine may be inducing undesired ketene formation due to the high acidity of the protons on the  $\alpha$  position.

Steglich first reported the use of carbodiimides in the presence of catalytic DMAP as a mild esterification method in 1978, noting that it was a natural extension of the well-established amide bond formation.<sup>78</sup> This method was

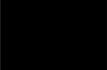
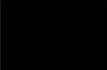
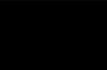
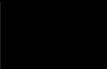
evaluated using diisopropylcarbodiimide with catalytic DMAP (entry 3). Analysis of the  $^1\text{H}$  NMR of the crude mixture showed presence of desired product, but also inseparable, unidentifiable impurities. Repeating the reaction in the presence of stoichiometric DMAP resulted in a complex mixture with no apparent desired product.

The coupling reagent 2-chloro-1-methylpyridinium iodide, or more commonly known as Mukaiyama's reagent, was developed in the 1970's to address the lack of mild esterification methods that utilized equimolar amounts of free carboxylic acid and alcohol.<sup>79,80</sup> The existing methods at that time included

Table 3.3. Summary of attempted esterification via carboxylic acid.

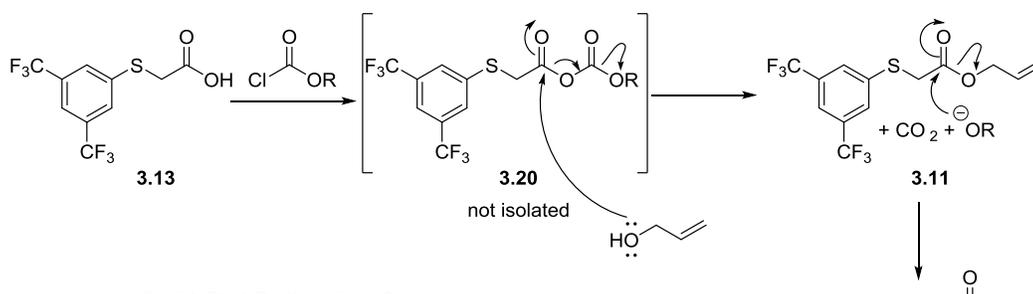


Entry	Starting Material	Coupling agent	Equiv. Allyl Alcohol	Conditions	Result
1	<b>3.14</b>	None	3	$\text{K}_2\text{CO}_3$ (5 equiv.); $\text{CH}_2\text{Cl}_2$ (0.6 M), 0 – 23 °C, 18 h	<b>3.11</b> (40% yield)
2	<b>3.14</b>	None	3	Py (2 equiv.), DMAP (0.1 equiv.), $\text{CH}_2\text{Cl}_2$ (0.6 M), 0 – 23 °C, 18 h	Variable yields of <b>3.11</b> (40-60%)
3	<b>3.13</b>	[REDACTED] (1.0 equiv.)	3	DMAP (0.1 equiv.), $\text{CH}_2\text{Cl}_2$ (0.1 M), 0 – 23 °C, 18 h	Mainly <b>3.11</b> but inseparable impurities present
4	<b>3.13</b>	[REDACTED] (1.0 equiv.)	3	DMAP (1.0 equiv.), $\text{CH}_2\text{Cl}_2$ (0.1 M), 0 – 23 °C, 18 h	No <b>3.11</b> obtained
5	<b>3.13</b>	[REDACTED]	1	$\text{NEt}_3$ (2.4 equiv.), $\text{CH}_2\text{Cl}_2$ (0.3 M), 40 °C, 4 h	Trace <b>3.11</b> with other allylated species

		(1.2 equiv.)			
6	<b>3.13</b>	 (1.0 equiv.)	3	Py (2 equiv.), DMAP (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), 0 – 23 °C, 18 h	14 : 86 <b>3.11 : 3.17</b>
7	<b>3.13</b>	 (1.0 equiv.)	3	Py (2 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), 0 – 23 °C, 18 h	Only <b>3.17</b>
8	<b>3.13</b>	 (1.0 equiv.)	3	Py (2 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), 0 – 23 °C, 4 h	10 : 90 <b>3.11 : 3.18</b> + unidentifiable impurities
9	<b>3.13</b>	 (1.0 equiv.)	3	Py (2 equiv.), DMAP (0.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), 0 – 23 °C, 4 h	12 : 88 <b>3.11 : 3.18</b> + unidentifiable impurities
10	<b>3.13</b>	Boc <sub>2</sub> O (1.1 equiv.)	3	Py (2 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), 0 – 23 °C, 18 h	70 : 30 <b>3.11 : 3.19</b> + unidentifiable impurities
11	<b>3.13</b>	Boc <sub>2</sub> O (1.1 equiv.)	3	Py (2 equiv.), DMAP (1.0 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), 0 – 23 °C, 18 h	9 : 91 <b>3.11 : 3.19</b> + unidentifiable impurities
12	<b>3.13</b>	 (1.0 equiv.)	3	Py (2 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), 0 – 23 °C, 18 h	74 : 26 <b>3.11 : 3.13</b>
13	<b>3.13</b>	 (1.0 equiv.)	3	Py (2 equiv.), DMAP (1.0 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), 0 – 23 °C, 18 h	79 : 21 <b>3.11 : 3.13</b>
14	<b>3.13</b>	 (1.0 equiv.)	3	Py (2 equiv.), DMAP (1.0 equiv.), CH <sub>2</sub> Cl <sub>2</sub> (0.1 M), reflux, 18 h	74% isolated <b>3.11</b>

TsCl, TFA and DCC, but each typically required 2-15 equivalents of the condensation reagent. Mukaiyama's methodology was applied to the free carboxylic acid **3.13** with 3 equivalents of allyl alcohol (entry 5). A small amount of the desired product was observed by <sup>1</sup>H NMR, combined with a large amount of unidentifiable impurities.

We then turned to preparation of mixed anhydrides to obtain allyl esters. Ethyl chloroacetate gave exclusively the ethyl ester, presumably by the mechanism shown in Scheme 3.6, in both presence and absence of catalytic DMAP. A similar result was obtained for phenyl chloroacetate, yielding exclusively the phenyl ester. Even attempts at using  $\text{Boc}_2\text{O}$  to form the ester via a mixed *t*-butyl anhydride resulted in *t*-butyl alkoxide acting as a nucleophile and the *t*-butyl ester was the only observed product.



Scheme 3.6. Mechanism of mixed anhydride formation, esterification and byproduct formation.

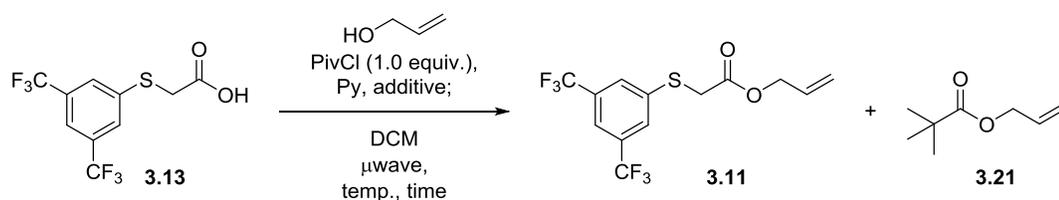
It became clear that the presence of any reasonable nucleophile would displace the allyl group. We envisioned using pivaloyl chloride to form the mixed anhydride. The by-product, the pivalate anion, would be poorly nucleophilic. Initial attempts at the reaction (entries 12 and 13) gave encouraging results, yielding 74 – 79% of desired product by  $^1\text{H}$  NMR, with the main byproducts being starting carboxylic acid, allyl pivalate and pivalic acid. The allyl pivalate and carboxylic acid are the result of nucleophilic attack on the other carbonyl of the mixed anhydride. When the reaction was repeated on larger scale with the conditions from entry 13, the desired product was isolated in a 74% yield (entry 14).

### 3.3 Development of New Esterification Method

#### 3.3.1 Reaction Optimization

Following the promising lead of the use of pivaloyl chloride, this reaction was optimized (Table 3.4). We elected to use DCM as solvent after screening the reaction in THF, toluene, Et<sub>2</sub>O and DCM. Ideally, we desired a much shorter reaction time than the 18 h that was currently necessary. Microwave heating in sealed reaction vessels proved an ideal method. Additionally, we anticipated that we could lower the number of equivalents of allylic alcohol that were required.

Table 3.4. Optimization of esterification via mixed pivalic anhydride.



Entry	Equiv ROH	Additive	Equiv Py	Temp (°C)	Time (min)	Conc (M)	Ratio <sup>a</sup>	Isolated Yield (%)
1	2.0	10 mol% DMAP	2	100	10	0.1	70:30	nd
2	1.0	10 mol% DMAP	2	100	10	0.1	71:29	nd
3	1.0	none	2	100	10	0.1	79:21	58
4	1.0	none	2	120	10	0.1	74:26	nd
5	1.0	none	2	100	10	0.25	72:28	66
6	1.0	none	2	100	10	0.5	77:23	69
7	1.0	none	2	100	10	1.0	81:19	60
8	1.0	none	1	100	10	0.5	61:39	50
9	1.0	none	2 <sup>b</sup>	100	10	0.5	84:16	nd
10	1.0	none	2	60	180	0.5	84:16	78
11	1.0	none	2	80	90	0.5	89:11	83
12	1.0	none	2	80	45	0.5	83:17	81
13	1.0	none	2	80	30	0.5	86:14	79
14	1.25	none	2	80	90	0.5	86:14	74
15	1.25	none	2	80	180	0.5	81:19	68

<sup>a</sup> Determined by <sup>1</sup>H NMR

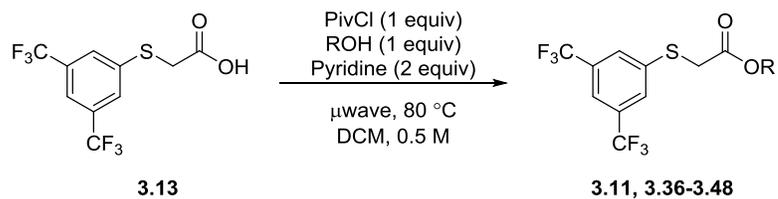
<sup>b</sup> 2-Chloropyridine was used in place of pyridine

The initial attempt using microwave heating (entry 1) used 2.0 equivalents of allyl alcohol and 10 mol% DMAP at 100 °C for 10 minutes. The results were quite comparable to those obtained with the initial reaction. We were successful in lowering the number of equivalents of alcohol required to 1.0 (entry 2) with a small improvement in selectivity. Under the same conditions, but omitting DMAP, improved the selectivity even further (entry 3). Increasing the temperature to 120 °C did not improve selectivity (entry 4). The optimal concentration was found to be 0.5 M (entries 3, 5-7). We chose to proceed with a concentration of 0.5 M due to higher isolated yield, despite the better regioselectivity with 1.0 M (entry 7). The use of only 1.0 equivalents of pyridine was very detrimental to the isolated yield (entry 8), while evaluation of the less basic 2-chloropyridine (entry 9) proved unsuccessful. The temperature and time were fully optimized (entries 10-13), finding that 80 °C and 45-90 minutes giving the highest isolated yield. Finally, using a slight excess of allyl alcohol was evaluated with longer reaction times (entries 14 and 15), however the isolated yields did not improve; in fact, they dropped.

This methodology permits the coupling of carboxylic acids and allylic or propargylic alcohols directly, without the formation of the corresponding halides or haloformate compounds. There are a wide variety of commercially available allylic and propargylic alcohols, whereas the halides are typically limited to simple allyl and propargyl groups and are relatively unstable. It is noteworthy that most literature methods for forming allylic esters from the corresponding allyl alcohols involve several equivalents of alcohol or even using the alcohol as solvent. This methodology allows the use of a 1:1 molar ratio of acid to alcohol, thereby

minimizing cost and waste. This is useful for very valuable allylic alcohols in which use of excess alcohol would be highly undesirable.

Table 3.5. Substrate scope of esterification via mixed pivalic anhydride formation (BTMP sulfides).

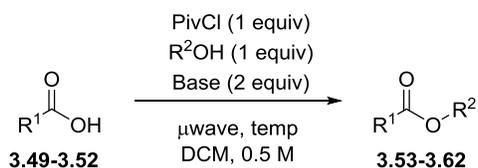


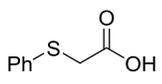
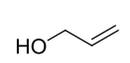
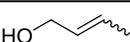
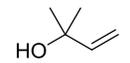
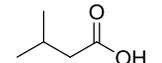
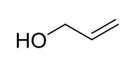
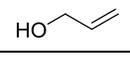
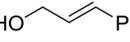
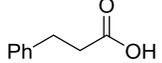
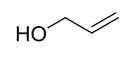
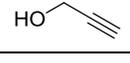
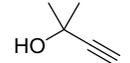
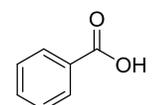
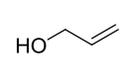
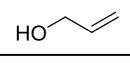
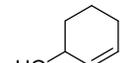
Entry	ROH	Time (min)	Yield <sup>a</sup> (%)	Product	
1	<chem>HOCH2CH=CH2</chem>	<b>3.22</b>	45	81	<b>3.11</b>
2	<chem>HOCH2CH=CH2</chem>	<b>3.22</b>	45	86 <sup>b</sup>	<b>3.11</b>
3	<chem>HOCH2C(CH3)=CH2</chem>	<b>3.23</b>	90	80	<b>3.36</b>
4	<chem>HOCH2CH=CHCH2CH3</chem>	<b>3.24</b>	45	75	<b>3.37</b>
5	<chem>HOCH2CH=CHPh</chem>	<b>3.25</b>	120	76	<b>3.38</b>
6	<chem>HOCH2C1=CCCCC1</chem>	<b>3.26</b>	120	78	<b>3.39</b>
7	<chem>HOCH2C(CH3)2=CH2</chem>	<b>3.27</b>	120	73	<b>3.40</b>
8	<chem>HOCH2CH(CH3)=CH2</chem>	<b>3.28</b>	120	65	<b>3.41</b>
9	<chem>HOCH2CH(CH3)CH=CHPh</chem>	<b>3.29</b>	120		<b>3.42</b>
10	<chem>HOCH2CH=CHCH2CH2Ph</chem>	<b>3.30</b>	90	63	<b>3.43</b>
11	<chem>HOCH2CH=CHC(CH3)2</chem>	<b>3.31</b>	90	70	<b>3.44</b>
12	<chem>HOCH2CH=CHCH2CH2CH=CHC(CH3)2</chem>	<b>3.32</b>	90	74	<b>3.45</b>
13	<chem>HOCH2CH=CHCH2CH=CH2</chem>	<b>3.33</b>	90	68	<b>3.46</b>
14	<chem>HOCH2CH2C#CH</chem>	<b>3.34</b>	45	74	<b>3.47</b>
15	<chem>HOCH2C(CH3)2C#CH</chem>	<b>3.35</b>	180	56	<b>3.48</b>

<sup>a</sup> Isolated yield

<sup>b</sup> Performed on 2.0 g (6.6 mmol) of **3.13**

Table 3.6. Substrate scope of esterification via mixed pivalic anhydride formation (other carboxylic



Entry	R <sup>1</sup> CO <sub>2</sub> H	R <sup>2</sup> OH	Base	Conditions	Yield <sup>a</sup> (%)	Product
1	 <b>3.49</b>	 <b>3.22</b>	Pyridine	80 °C, 90 min	76	<b>3.53</b>
2		 <b>3.24</b>	Pyridine	80 °C, 90 min	73	<b>3.54</b>
3		 <b>3.27</b>	Pyridine	80 °C, 180 min	50	<b>3.55</b>
4	 <b>3.50</b>	 <b>3.22</b>	Pyridine	80 °C, 90 min	0	<b>3.56</b>
5		 <b>3.22</b>	DMAP	100 °C, 45 min	25 <sup>b</sup>	<b>3.56</b>
6		 <b>3.25</b>	DMAP	100 °C, 45 min	75	<b>3.57</b>
7	 <b>3.51</b>	 <b>3.22</b>	DMAP	100 °C, 45 min	76	<b>3.58</b>
8		 <b>3.34</b>	DMAP	100 °C, 90 min	71	<b>3.59</b>
9		 <b>3.35</b>	DMAP	100 °C, 180 min	68	<b>3.60</b>
10	 <b>3.52</b>	 <b>3.22</b>	Pyridine	80 °C, 90 min	32	<b>3.61</b>
11		 <b>3.22</b>	DMAP	100 °C, 45 min	63	<b>3.61</b>
12		 <b>3.26</b>	DMAP	100 °C, 120 min	66	<b>3.62</b>

<sup>a</sup> Isolated yield

<sup>b</sup> Low isolated yield attributed to volatility of **3.56**

### 3.3.2 Substrate Scope

The scope of the esterification reaction was explored using the optimized conditions (Table 3.5 and Table 3.6). The reaction was found to be amenable to scale-up (entry 2), giving a high yield (86%) for 2.0 g (6.6 mmol) of starting carboxylic acid. A variety of substituted allylic alcohols were successfully coupled to **3.13**. Entries 3-5 demonstrate the viability of 2- and 3-substituted primary allylic alcohols in the reaction. Secondary and tertiary allylic alcohols are also viable coupling partners. Longer reaction times were required for electron-poor and sterically demanding allylic alcohols to attain similar yields as for allyl alcohol.

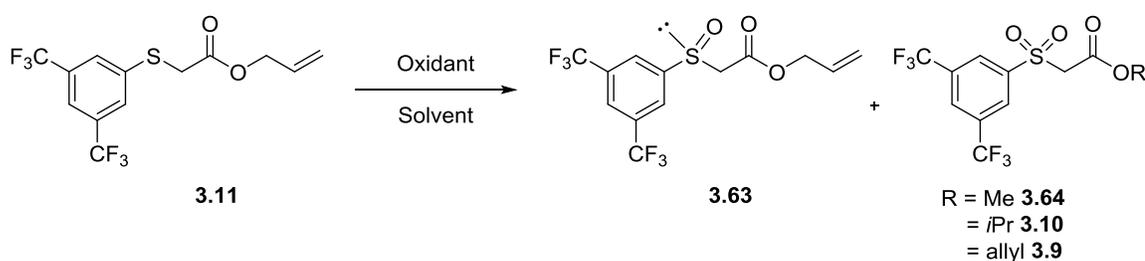
The role of the electronics of the carboxylic acid were also examined (Table 3.6). The use of the analogous  $\alpha$ -thiophenylacetic acid (entries 1-3) was found to have similar reactivity to the 3,5-BTMP sulfone. However, the reaction was completely shut down when a more electron-neutral carboxylic acid was used. Isovaleric acid and allyl alcohol, under the optimized conditions, gave no desired product (entry 4). The reactivity was restored, however, by the use of a stronger base (DMAP) and a higher temperature (100 °C) (entry 5).

Given the simplicity and ease of this methodology, coupled with its low cost, we published this work in 2013.<sup>81</sup>

### 3.4 Optimization of Oxidation

Having secured a viable route to allylic sulfide esters, attention was turned to oxidation of the sulfide (Table 3.7). It was anticipated that judicious choice of reagent would be required to avoid chemoselectivity issues (such as alkene epoxidation), as well as prevent nucleophilic attack on the allyl ester carbonyl. We elected to begin with treatment with Oxone in MeOH/water, as was performed for

Table 3.7. Optimization of oxidation conditions.



Entry	Catalyst/Oxidant	Solvent	Result
1	Oxone	MeOH	SM Decomp.
2	FeCl <sub>3</sub> (cat), H <sub>5</sub> IO <sub>6</sub>	MeCN	<b>3.63</b> exclusively
3	MnSO <sub>4</sub> (cat), H <sub>2</sub> O <sub>2</sub>	MeCN	Mixture of <b>3.63</b> & <b>3.9</b>
4	(NH <sub>4</sub> ) <sub>6</sub> Mo <sub>7</sub> O <sub>24</sub> (cat), H <sub>2</sub> O <sub>2</sub>	MeOH	Mixture of <b>3.64</b> & <b>3.9</b>
5	(NH <sub>4</sub> ) <sub>6</sub> Mo <sub>7</sub> O <sub>24</sub> (cat), H <sub>2</sub> O <sub>2</sub>	<i>i</i> -PrOH	Mixture of <b>3.10</b> & <b>3.9</b>
6	(NH <sub>4</sub> ) <sub>6</sub> Mo <sub>7</sub> O <sub>24</sub> (cat), H <sub>2</sub> O <sub>2</sub>	<i>t</i> -BuOH	<b>3.9</b> exclusively

the ethyl ester in Nájera's work.<sup>70</sup> These reaction conditions were quite destructive to the substrate. There was no evidence of starting material remaining, however only a small amount of product could be obtained. The remaining material was a complex mixture of inseparable impurities.

Examination of the literature found several mild sulfide oxidation methodologies that had the potential to be selective for our substrate. Kim and co-

workers reported the oxidation of sulfides to sulfoxides by treatment with periodic acid and catalytic iron(III) chloride in acetonitrile.<sup>82</sup> Given the mildness of the conditions, they were evaluated for oxidation of compound **3.11**. The formation of the sulfoxide was clearly demonstrated by the diastereotopic CH<sub>2</sub> peaks in the <sup>1</sup>H NMR. Allowing the reaction to run longer was unsuccessful at promoting sulfone formation. However, the ability to form the sulfoxide selectively was useful, and we returned to this topic later on.

Nájera and co-workers developed a chemoselective sulfide oxidation that exhibited chemoselectivity in the presence of a variety of sensitive functional groups, including allyl groups.<sup>83</sup> There was also an example of oxidation of a 3,5-bis-trifluoromethylphenyl sulfide, albeit not with an allyl ester. Treatment of compound **3.11** in MeCN with catalytic manganese sulfate hydrate and superstoichiometric hydrogen peroxide, in the presence of NaHCO<sub>3</sub> buffer solution, gave a mixture of sulfoxide and sulfone.

Chand and co-workers reported the use of catalytic ammonium molybdate tetrahydrate with hydrogen peroxide as the re-oxidant to selectively oxidize sulfides to sulfones in the presence of a variety of sensitive functional groups.<sup>84</sup> This reagent combination features prominently in several sulfide oxidations on advanced intermediates in Evans' total synthesis of Azaspiracid-1, emphasizing the mildness of the reaction conditions.<sup>85</sup>

Gratifyingly, the use of catalytic ammonium molybdate tetrahydrate in methanol with hydrogen peroxide as re-oxidant resulted in clean conversion to the sulfone. Depending on the length of the reaction, however, variable amounts of transesterification to the methyl ester was observed. This issue was resolved by optimization of the solvent. While isopropyl alcohol continued to effect transesterification at a rate competitive with sulfide oxidation, tert-butyl alcohol completely suppressed this by-product formation. Regardless of the length of time over which the reaction was run, no tert-butyl ester was observed.

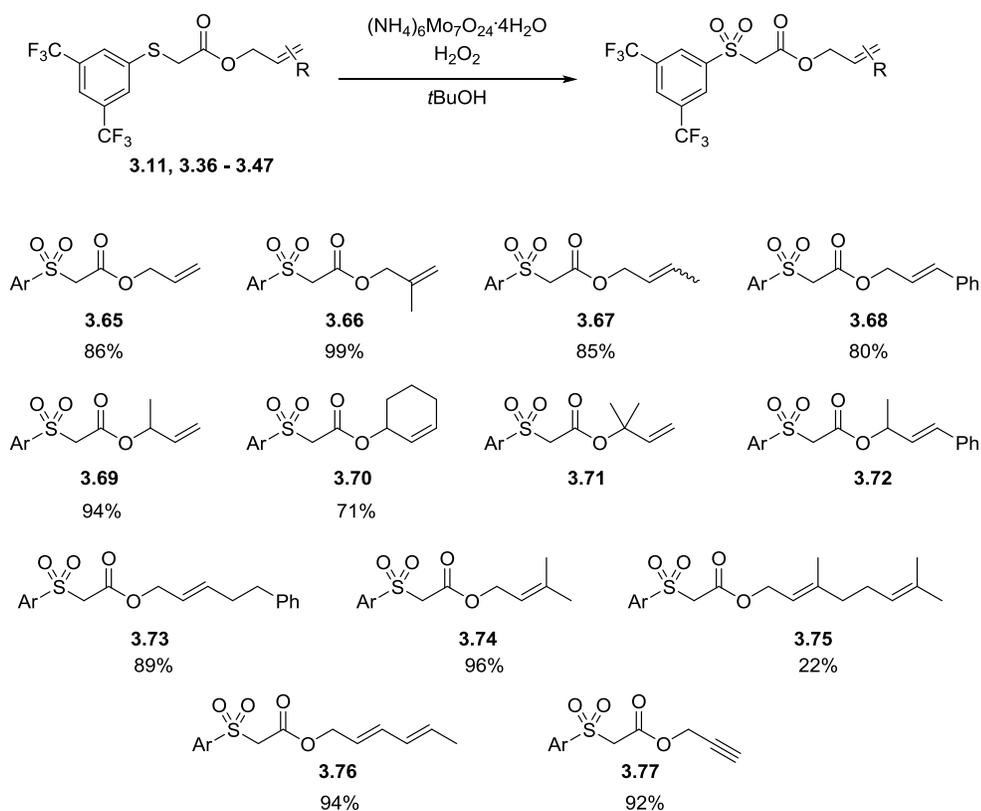


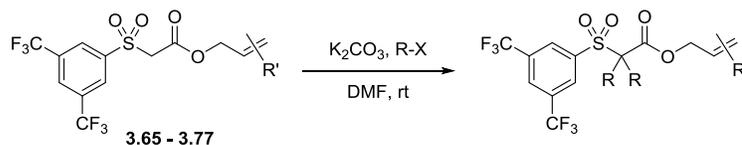
Figure 3.1. Substrate scope for sulfide oxidation.

A family of BTMP sulfones (Figure 3.1) was prepared in good to excellent yield using the optimized conditions. The exception was the geranyl ester substrate **3.75** which was obtained in only 22%. This result is attributed to poor solubility of the product in the work-up solvent. Gentle heating to improve solubility caused decomposition of the product. The purity of the crude products was very high and they were generally used in the next step without purification.

### **3.5 Optimization of Alkylation**

Nájera and co-workers had performed alkylations in THF with  $K_2CO_3$  and  $Bu_4NBr$ , however we found that these conditions were not consistent in giving high yields of dialkylated products. Varying amounts of monoalkylated products were typically isolated. Additionally, the tetrabutylammonium salts were occasionally

Table 3.8. Substrate scope for dialkylation (identical substituents).

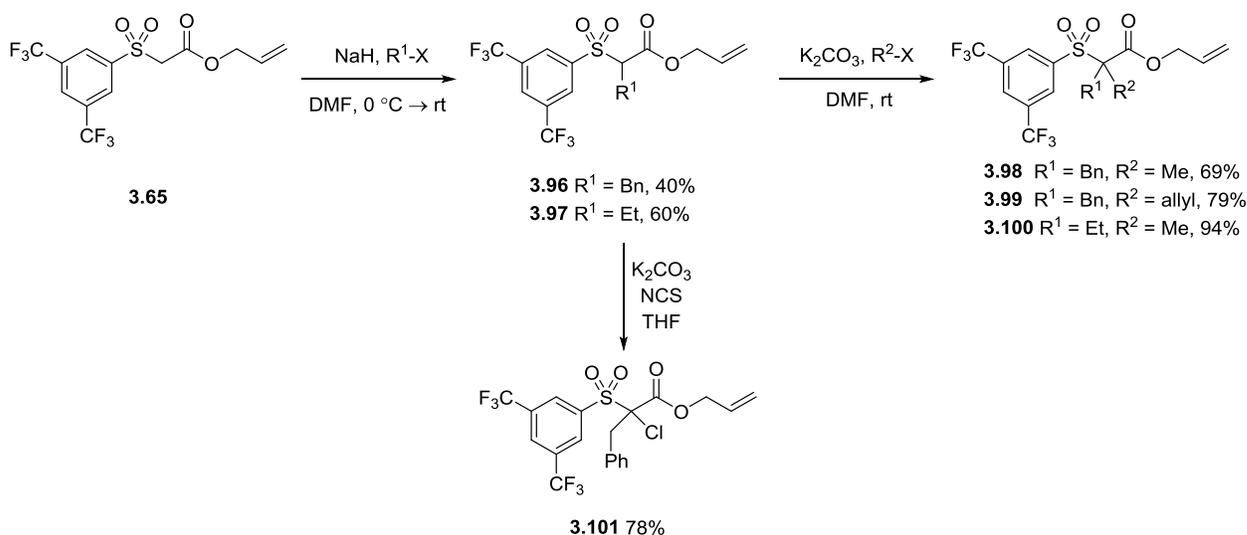


Entry	Substrate	Product	Yield (%)
1-8			R = Bn 98 R = Me 95 R = Et 92 R = Pr 48 R = hexyl 27 R = -(CH2)6- 27 R = allyl R = CH2CO2Et 53
9			90
10			94
11			75
12			89
13			74
14			86
15			84
16			90
17			87
18			

difficult to fully remove by chromatography. Similar to the findings of Tunge and Weaver in their studies of  $\alpha,\alpha$ -dialkylated phenylsulfones, optimal results for dialkylation were found using  $\text{K}_2\text{CO}_3$  and dry DMF.<sup>67</sup> The crude reaction mixtures

were typically quite clean and required column chromatography only to remove residual DMF and any residual alkyl halide. The yields were good to excellent, especially when activated electrophiles (such as benzyl bromide, methyl iodide, ethyl iodide, propyl iodide and allyl bromide) were employed (Table 3.8). For less activated electrophiles (such as hexyl bromide and 1,6-dibromohexane, entries 6-7), the yields were substantially reduced despite longer reaction times and the addition of tetrabutylammonium iodide.

The synthesis of differentially substituted  $\alpha,\alpha$ -dialkyl substrates was possible by a two-step procedure. As illustrated in Scheme 3.7, the anion of



Scheme 3.7. Synthesis of differentially substituted substrates.

sulfone **3.65** was generated using sodium hydride in DMF. Quenching of this anion with an alkyl halide resulted in a modest amount of monoalkylated product. It should be noted that this procedure is unoptimized. The second alkylation was performed under identical conditions as for dialkylated substrates ( $\text{K}_2\text{CO}_3$ ,  $\text{R-X}$ , DMF).

### 3.6 Early DcA Studies

Having developed a viable synthetic strategy towards appropriate substrates, a number of substrates were evaluated for their suitability in the palladium-catalyzed decarboxylative reaction. Using the same conditions that had been optimized for the analogous triflone compound, we were pleased to see that dibenzylated substrates gave the allylated compound in good yield, although not

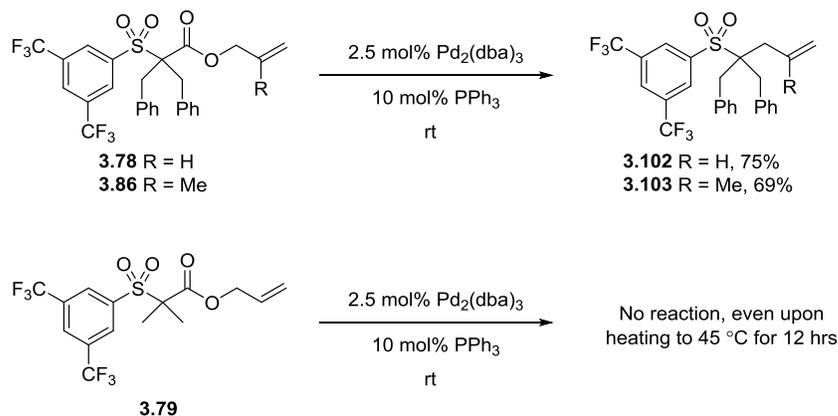
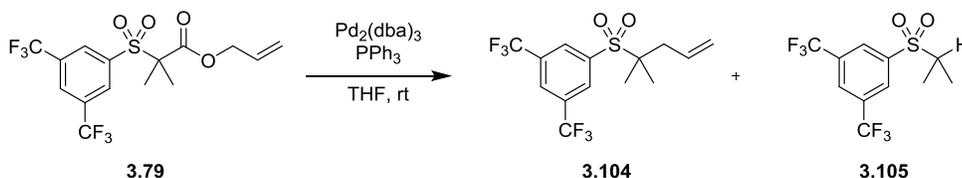


Figure 3.2. Initial DcA reactions of BTMP sulfones.

as high as for the triflones (Figure 3.2). We were surprised, however, when it was observed that the analogous dimethyl compounds were completely unreactive under the same conditions. Heating the reaction for 12 h at 45 °C did not promote

Table 3.9. Evaluation of effect of Pd : phosphine ratio.



Pd : P Ratio	3.79 (%)	3.104 (%)	3.105 (%)
1:2	52	35	13
1:3	16	16	68
1:4	0	0	100

the reaction at all. We evaluated a higher catalyst loading and the Pd:P ratio using PPh<sub>3</sub> (Table 3.9). Moderate quantities of desired product were formed after stirring overnight, however protonated product was also observed. The only effect observed from raising the Pd : phosphine ratio was increased formation of protonated product.

We elected to try to optimize reaction conditions that would allow for reactivity of the  $\alpha,\alpha$ -dimethyl substrate. A ligand-screening study was carried out (Table 3.10) and small quantities of a third product were observed. This product was eventually identified as the cyclopropyl adduct **3.106**. The highly shielded peaks in the <sup>1</sup>H NMR were consistent with the cyclopropyl product shown. Although formation of cyclopropyl products via allylation chemistry is known, it is rarely observed in intramolecular decarboxylative variants.

Hegedus and co-workers were the first to report the occurrence of cyclopropyl products as a result of palladium-catalyzed allylation processes (Figure 3.3). Treatment of the enolate of methyl cyclohexanecarboxylate with  $\pi$ -

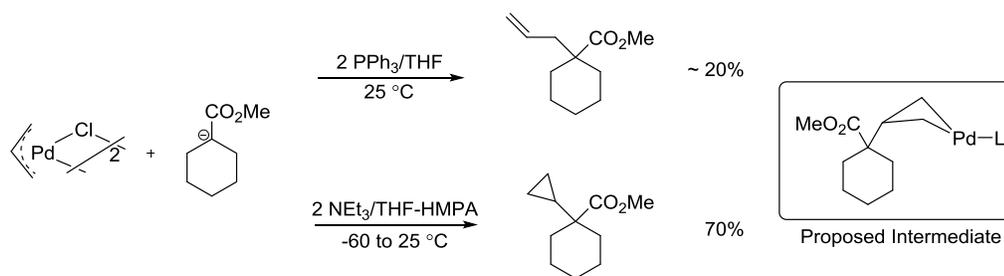


Figure 3.3 Seminal report of cyclopropane formation via allylation chemistry.

allyl palladium chloride dimer and PPh<sub>3</sub> in THF gave a low yield of allylated product. While exploring other reaction conditions in an attempt to promote a higher yield

of allylation, the corresponding cyclopropyl product was unexpectedly isolated. The experiment was repeated using 2-deuterio- $\pi$ -allyl palladium chloride dimer; incorporation of the deuterium label in the cyclopropyl product was exclusively at the carbon bound to the cyclohexane ring. This provided strong evidence that nucleophilic attack of the enolate occurred at the central carbon of the allyl moiety. Hegedus and co-workers proposed that a palladacyclobutane was an intermediate in the reaction, and that reductive elimination would result in the observed cyclopropyl product. All attempts made to trap the proposed intermediate failed, however it was noted that the presence of CO tended to increase the yield of the cyclopropyl product.

Hoffmann and co-workers expanded the substrate scope for this transformation.<sup>86,87</sup> Selected examples are shown in Figure 3.4 – depending on the substrate, an atmosphere of CO was required to achieve a reasonable yield.

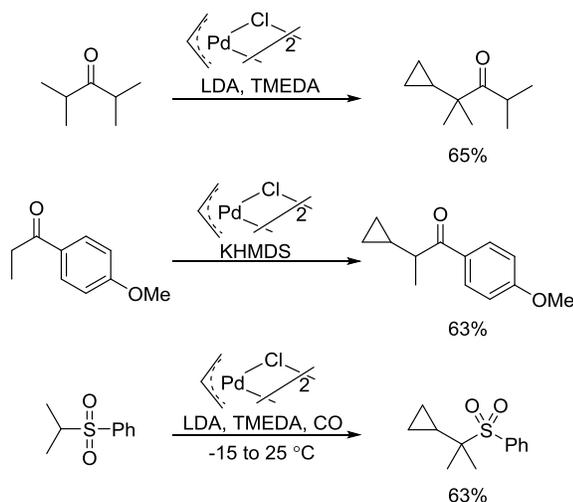
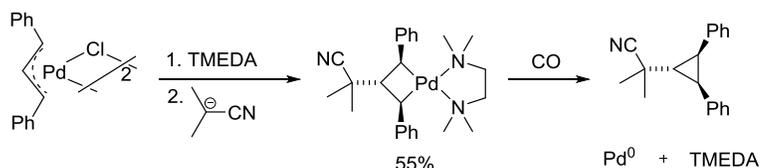


Figure 3.4. Selected examples of cyclopropane formation from Hoffmann.

Further to this work, Hoffmann was successful in isolating the palladacycle intermediate, providing further evidence for the proposed mechanism (Scheme

3.8).<sup>88</sup> The structure of the palladacycle was verified by X-ray crystallography. The compound was found to be kinetically inert at room temperature and was air and water stable. When the compound was exposed to an atmosphere of CO, the



Scheme 3.8. Isolation of palladacyclobutane intermediate.

corresponding cyclopropyl compound was obtained. Additional examples of cyclopropane formation from nucleophilic attack at allylic C-2 have been reported from Satake<sup>89,90</sup> and Hou<sup>91</sup>, yet those reports all involved *intermolecular* examples. No *intramolecular* decarboxylative variants were found in the literature.

The effect of varying the ligand on the product distribution was evaluated. Ligands can vary in their steric contribution to an active catalyst, as well as the electronic contribution. Steric parameters are often described by the Tolman cone angle  $\theta$ . This angle, as illustrated in Figure 3.5, is given by the angle of a cylindrical cone, just touching the van der Waals radii of the outermost atom, that is centered 2.28 Å from the center of the phosphorus atom. The electronic parameter of a

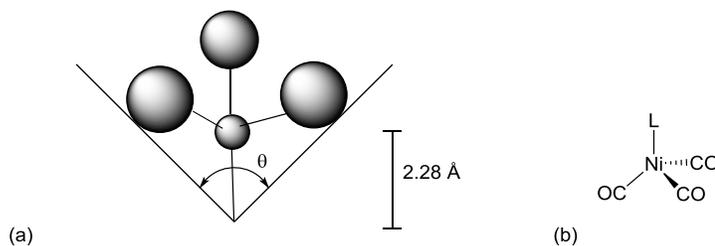


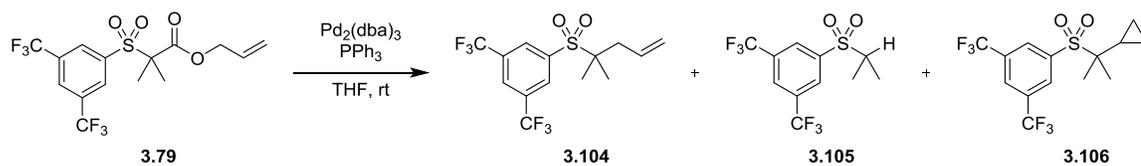
Figure 3.5. Tolman steric (a) and electronic (b) parameters.

phosphine ligand is generally measured as the carbonyl stretching frequency of

the corresponding Ni(0) complex composed of the ligand in question and CO ligands. The stretching frequency varies based on the electron-donating or withdrawing capabilities of the ligand on the metal center.

As shown in Table 3.10 and Figure 3.6, a variety of monodentate and bidentate ligands were screened. The ligands found to be successful in consuming all the starting material were BINAP, dppf, XANTPHOS, SEGPHOS and MeO-BIPHEP. All of these ligands are bidentate phosphines, however they have varying bite angles and electronic parameters. The use of a bidentate ligand seemed to be critical for activity. The ligands that yielded the highest amounts of allylated product were the same as the ligands that consumed all of the starting material, with the addition of DPEphos. Protonation was favored with the use of monodentate phosphines  $\text{PBU}_3$  and tris(2,6-methoxyphenyl)phosphine, as well as with TRIPHOS and dppb. None of the ligands evaluated promoted the cyclopropyl product as the dominant product. The best results came from the use of SEGPHOS and MeO-BIPHEP, which resulted in 19 and 21 % cyclopropyl product respectively. Unfortunately, none of these ligands were able to promote formation of the allylated product in a synthetically useful ratio.

Table 3.10. Ligand screening study for  $\alpha,\alpha$ -dimethyl substrates.



Ligand	3.79 (%)	3.104 (%)	3.105 (%)	3.106 (%)
DPEPhos <b>3.107</b>	7	46	39	8
dppb <b>3.108</b>	30	10	59	1
dppf <b>3.109</b>	0	38	53	11
BINAP <b>3.110</b>	0	41	47	12
<b>3.111</b>	65	8	25	2
XANTPHOS <b>3.112</b>	0	47	49	5
TRIPHOS <b>3.113</b>	32	6	62	0
$\text{P}(\text{2-furyl})_3$ <b>3.114</b>	100	0	0	0
$\text{PBu}_3 \cdot \text{HBF}_4 \cdot \text{K}_2\text{CO}_3$ <b>3.115</b>	72	5	23	0
SEGPPOS <b>3.116</b>	0	58	23	19
MeO-BIPHEP <b>3.117</b>	0	63	16	21
<b>3.118</b>	53	0	47	0

The ligand screening was performed at room temperature in an attempt to

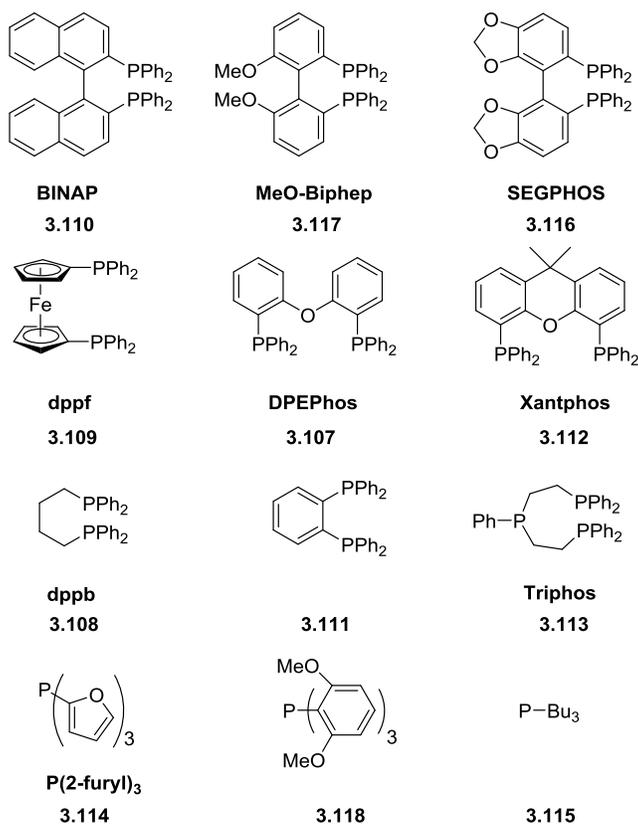
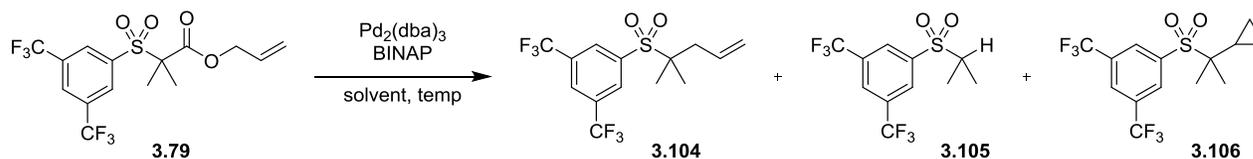


Figure 3.6. Structure of ligands used in screening.

determine comparable reaction conditions to the exceptionally reactive triflone substrates. However, due to the lack of success in finding a suitable ligand that promoted allylation exclusively at room temperature, we elected to examine the effect of raising the reaction temperature. The ligand BINAP had given the most promising results and it was chosen for the temperature study. Shown in the same table (Table 3.11) is the results of a solvent screen for the same reaction.

Table 3.11. Evaluation of temperature and solvent with BINAP for  $\alpha,\alpha$ -dimethyl substrate.

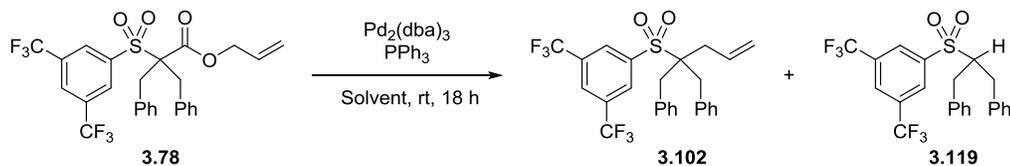


Solvent	Temperature (°C)	3.79 (%)	3.104 (%)	3.105 (%)	3.106 (%)
THF	rt	0	41	47	12
THF	40	5	64	14	17
THF	65	0	75	7	18
Et <sub>2</sub> O	rt	0	64	21	15
DCM	rt	80	4	15	1
toluene	rt	0	75	13	12

### 3.7 Optimization of DcA for dibenzyl substrate Pd<sub>2</sub>(dba)<sub>3</sub>

Despite a great deal of effort, the product distribution for the dimethyl substrate was not able to be shifted towards allylated product in a synthetically useful ratio. We began to wonder if there was something unusual about the dimethyl substrate itself, and that other substrates would lend themselves better to the process. We returned to the dibenzyl substrate and performed an extensive solvent screen (Table 3.12). The results for ethereal based solvents (THF, Et<sub>2</sub>O, DME and MTBE) were particularly promising. The promising lead results were repeated, however some troubling observations were made during the course of these experiments; the results were not reproducible.

Table 3.12. Solvent screen for  $\alpha,\alpha$ -dibenzyl substrate.



Solvent	3.78 (%)	3.102 (%)	3.119 (%)
THF	0	79	21
Et <sub>2</sub> O	0	91	9
DCM	6	67	27
Toluene	9	6	85
DME	3	74	23
DCE	66	0	34
MeCN	73	0	27
DMF	11	0	89
1,4-Dioxane	18	61	18
MTBE	0	90	10

\*Ratio determined from crude <sup>1</sup>H NMR integration ratios measured against p-cymene standard

Focus was placed on reproducibility of results with a single solvent. The reaction was repeated in THF in multiple side-by-side reactions under identical conditions. Some experiments gave substantially different ratios of allylated to protonated products, while others simply didn't react at all. It was noted that some reaction mixtures appeared to produce more Pd black deposits than others, but this observation didn't correlate with experimental results and product distribution. Extensive experimentation was performed in an attempt to obtain consistent results, including degassing solvent, performing reaction in dark and *exhaustive* glassware cleaning.

### 3.8 Issues with Pd<sub>2</sub>(dba)<sub>3</sub> and Investigation of Baird Catalyst

Given the issues that were being experienced and that all other attempts to control variables had not yet revealed the nature of the inconsistent results, we decided to take a close look at the palladium source. Dipalladium trisbenzylidene

acetone had been chosen simply due to its prevalent use in the palladium catalyzed DcA literature. Examination of the primary literature with regards to this widely used pre-catalyst, however, revealed some potential issues.

### 3.8.1 Incomplete dissociation of dibenzylidene acetone

Amatore and Jutand have reported a number of detailed studies using  $^{31}\text{P}$  NMR and electrochemical methods to examine the generation of active Pd(0) species from Pd(dba)<sub>2</sub> and phosphine ligands.<sup>92</sup> The role of dba in the reactivity of these species was determined to be extremely important. In the case of

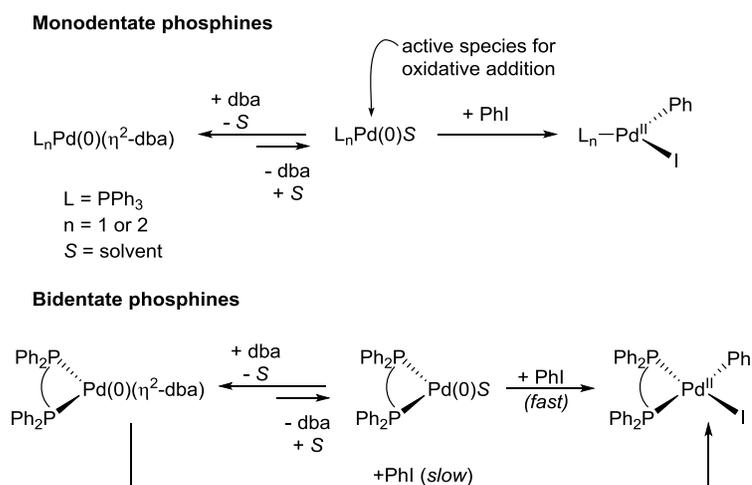


Figure 3.7. Effect of dba ligand on generation of active Pd(0) catalysts.

monodentate phosphines, such as PPh<sub>3</sub>, an equilibrium exists between the active species for oxidative addition and the catalyst with coordinated dibenzylidene acetone (Figure 3.7). Unfortunately, this equilibrium lies towards the  $\eta^2$ -dba coordinated palladium species. Choice of solvent is crucial to promote displacement of the dba ligand.<sup>93</sup>

In the case of bidentate phosphine ligands, such as BINAP, a similar equilibrium exists between solvated active Pd(0) complex and  $\eta^2$ -dba coordinated complex, however the kinetics are complicated by the fact that both of these species are capable of catalyzing the oxidative addition step. The solvated species is a substantially more competent catalyst for oxidative addition, but the equilibrium lies towards the  $\eta^2$ -dba coordinated complex.<sup>94</sup>

Fairlamb has reported extensively on the preparation and catalytic activity of 4-substituted dba analogues. Much of this work, along with related references, is summarized in his 2008 perspective.<sup>95</sup> As illustrated in Figure 3.8, the presence of alkene ligands complicates the catalytic cycle of a typical cross coupling reaction. The center cycle is the traditional mechanism in which oxidative addition yields a Pd(II) intermediate, which then undergoes transmetalation and subsequent reductive elimination to yield the cross-coupled product. In reality, however, the dba ligand may be involved in both, one or neither of the oxidative addition and the reductive elimination steps. These competing pathways complicate mechanistic studies, as each step has its own kinetics. However, presence of dba (or one of its analogues) can actually be beneficial. For reactions in which  $\beta$ -hydrogen elimination is undesirable, for example, the step can be slowed by  $\pi$ -acidic alkenes.

While the issues with incomplete dissociation of dba do not explain the inconsistent results that had been obtained, they were an important consideration while trying to optimize the DcA reaction. The next section describes what is believed to be the root cause of the inconsistent results.

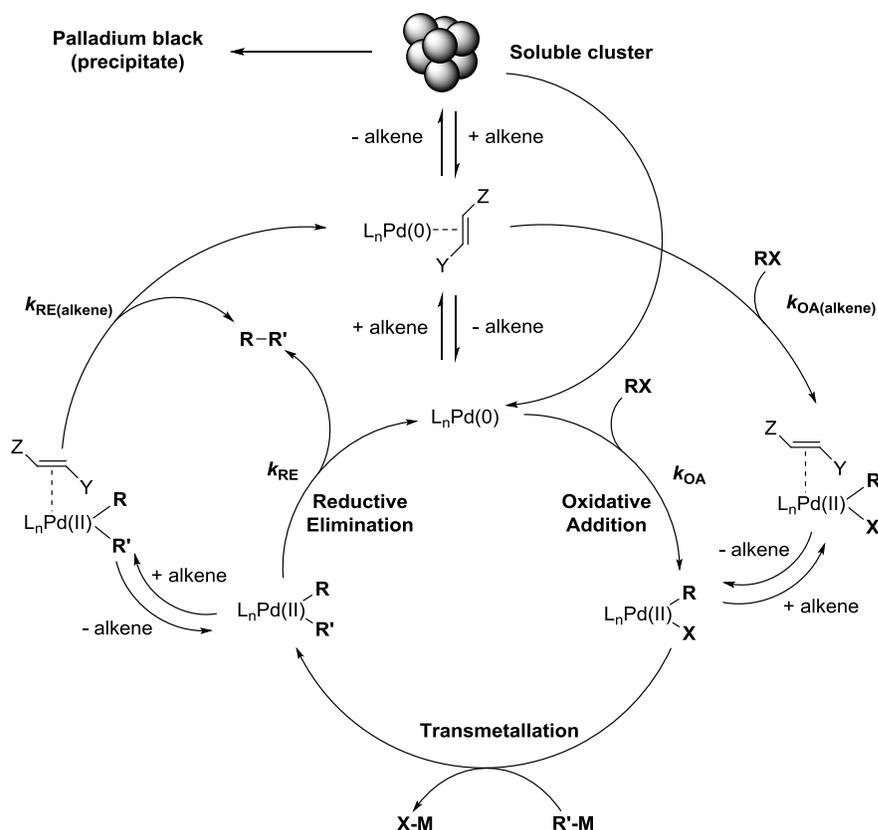


Figure 3.8. Mechanism of cross-coupling with and without dba.

### 3.8.2 Pd nanoparticles

In the course of trying to understand the solution structure of  $\text{Pd}_2(\text{dba})_3$ , Zaleskiy and Ananikov made some remarkable observations.  $^1\text{H}$  DOSY spectroscopy revealed that, depending on the pre-catalyst sample, there was varying amounts of free dba ligand. This was unexpected, as the crystal structure of  $\text{Pd}_2(\text{dba})_3$  has shown coordination of all six alkenes to the two Pd atoms. Also, the sample was prepared in  $\text{CDCl}_3$ , which would not be expected to displace dba. The free ligand in solution was attributed to decomposition of  $\text{Pd}_2(\text{dba})_3$  to

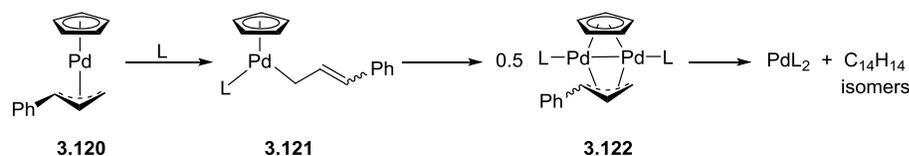
palladium metal and free dba. An operationally simple  $^1\text{H}$  NMR assay for  $\text{Pd}_2(\text{dba})_3$  was developed and applied.<sup>96</sup>

Detailed analysis of  $\text{Pd}_2(\text{dba})_3$  samples revealed a remarkable variability in purity. Samples from three different commercial suppliers were found to have purity of 77, 92 and 64%. Freshly prepared samples quickly dropped off in purity from 99% when stored in the solid state. An even more troubling result was obtained upon analysis of the palladium metal isolated from the samples. ICP-MS analysis confirmed that the sample was palladium, however field emission scanning electron microscopy of the material revealed that it was a complex mixture of metal particles. A broad range of particle sizes (60 – 200 nm) were observed, as well as some small nanoparticles (~ 10 - 20 nm). Most of the particles were round or rectangular with rounded edges. Some agglomeration into microstructures was observed.

The presence of such complicated mixtures in catalysts which are generally used as received raises important questions. How can we distinguish between homogenous catalysis, heterogeneous catalysis, or even catalysis via leaching from a solid phase? Are all three happening simultaneously? Ananikov has elaborated on these ideas in two excellent papers.<sup>97,98</sup> The  $^1\text{H}$  NMR assay described by Ananikov was performed on a sample of the  $\text{Pd}_2(\text{dba})_3$  that had been in use most recently in the optimization studies. The results were startling – triplicate analysis found that the catalyst was ~ 45% pure. Given the potential issues from the presence of dba, coupled with the highly variable nature of  $\text{Pd}_2(\text{dba})_3$ , we elected to explore the used of other palladium pre-catalysts.

### 3.8.3 Baird Catalyst

While considering other potential palladium pre-catalysts, we noted a series of reports from Baird. He had successfully developed a Pd(II) pre-catalyst, Pd( $\eta^3$ -1-PhC<sub>3</sub>H<sub>4</sub>)( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>) and has been shown to cleanly reduce to Pd(0) catalysts with a variety of phosphine ligands and solvents (Scheme 3.9).<sup>99</sup> The analogous allyl-



Scheme 3.9. Use of Pd( $\eta^3$ -1-PhC<sub>3</sub>H<sub>4</sub>)( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>) **3.120** as Pd(0) pre-catalyst.

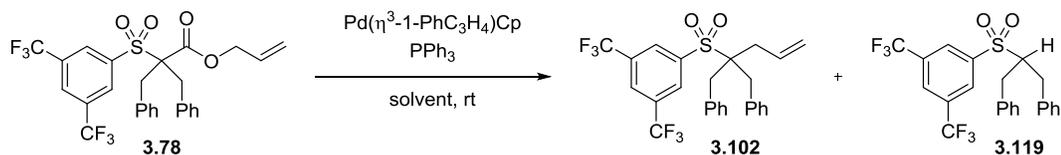
based Pd(II) complex has been long known, but wasn't widely used in Pd catalysis due to its volatility and thermal instability. The cinnamyl-based analogue solved those issues. The Baird research group had demonstrated superior catalyst performance for Pd( $\eta^3$ -1-PhC<sub>3</sub>H<sub>4</sub>)( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>) in comparison to Pd<sub>2</sub>(dba)<sub>3</sub>/PPh<sub>3</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> in Suzuki-Miyaura,<sup>100</sup> Sonogashira,<sup>101</sup> and Heck-Mizoroki<sup>102</sup> cross-couplings, as well as in Buchwald-Hartwig aminations.<sup>103</sup> We elected to evaluate this pre-catalyst for our DcA reaction.

### 3.9 Re-Optimization of DcA for dibenzyl substrate with Baird Catalyst

A solvent screen using PPh<sub>3</sub> at room temperature was performed as a starting point with this new pre-catalyst (Table 3.3). We were pleased to observe that THF and Et<sub>2</sub>O yielded over 80% each of allylated product (as determined by <sup>1</sup>H NMR) in short reaction times at room temperature. Of even greater importance, however, was that the reactivity and product ratios were reproducible! The use of acetonitrile yielded exclusively protonated product, which is a typical result in Pd-

catalyzed DcA reactions. We elected to proceed with the optimization using THF to allow for greatest possible temperature range. Two experiments were performed in which the concentration in THF was halved and doubled. In each case, the % allylated product dropped substantially. When the concentration was halved, 78% allylated was obtained, while doubling the concentration yielded 52% allylated product (the balance of the product in each case was protonated product).

Table 3.13. Solvent screening results for DcA reaction using (1-cinnamyl)PdCp.



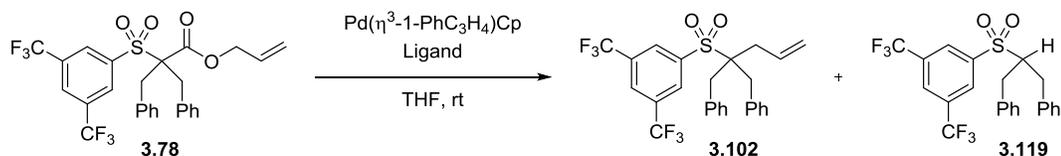
Solvent	<b>3.78</b> (%)	<b>3.102</b> (%)	<b>3.119</b> (%)
THF	0	81	19
Et <sub>2</sub> O	0	82	18
Toluene*	88	0	12
DCM	0	33	67
1,4-Dioxane*	90	0	10
DCE*	90	0	10
MeCN	0	0	100
DME*	25	0	75
MTBE*	90	0	10

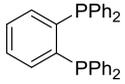
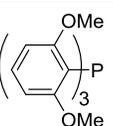
\* Heated to 50°C for 18 h after no progress at rt

% determined by <sup>1</sup>H NMR of crude reaction mixtures

Using THF as a solvent, a detailed ligand screening was undertaken to determine optimal conditions to favor the allylated over the protonated product (Table 3.14). The selection of ligands was based on evaluating the effect of steric bulk and electronics (Figure 3.9). Many ligands were not useful in promoting

Table 3.14. Ligand screening results for (1-cinnamyl)PdCp in THF.



Ligand	3.78 (%)	3.102 (%)	3.119 (%)
PPh <sub>3</sub>	0	81	19
BINAP <b>3.110</b>	0	43	57
MeO-BIPHEP <b>3.117</b>	5	16	79
XANTPHOS <b>3.112</b>	0	81	19
dppf <b>3.109</b>	66	0	34
DPEphos <b>3.107</b>	89	0	11
SEGPPOS <b>3.116</b>	0	8	92
CyJohnPhos <b>3.123</b>	84	0	16
P(2-furyl) <sub>3</sub> <b>3.114</b>	77	0	23
dppb <b>3.108</b>	>99	0	trace
 <b>3.111</b>	0	0	100
PBu <sub>3</sub> ·HBF <sub>4</sub> <b>3.115</b>	92	0	8
 <b>3.118</b>	59	0	41
DACH <b>3.124</b>	>99	0	trace
<i>i</i> Pr-PHOX <b>3.125</b>	84	0	16

% determined by <sup>1</sup>H NMR of crude reaction mixtures

complete consumption of the starting material. Almost all ligands in which starting material remained after 18 h reaction time yielded only protonated product. The ligands MeO-BIPHEP, SEGPHOS and 1,2-bis(diphenylphosphine)benzene gave predominantly or exclusively the protonated product. The most promising results were observed with XANTPHOS and PPh<sub>3</sub>, which both resulted in 81% allylated product. By increasing the reaction temperature to 50 °C using the ligand XANTPHOS, we observed a 92:8 ratio of allylated to protonated products. Using these optimized conditions, the substrate scope for this reaction was evaluated.

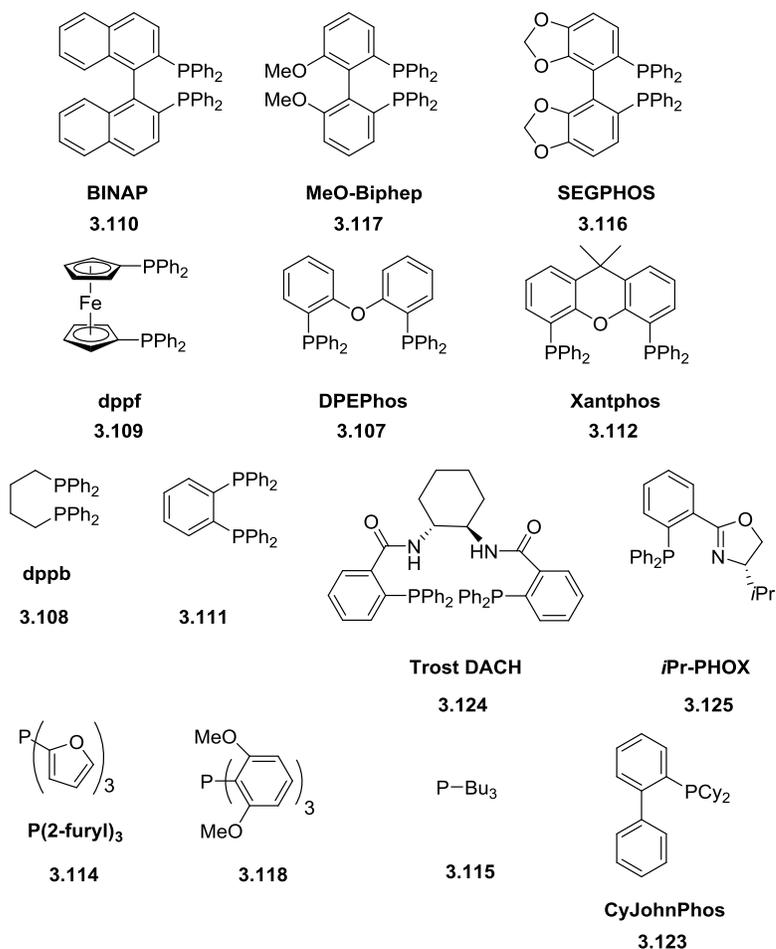
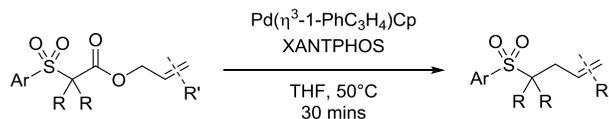


Figure 3.9. Structure of ligands used in ligand screening.

### 3.10 Evaluation of Substrate Scope

As illustrated in Figure 3.10, it was found that  $\alpha,\alpha$ -dialkylated allylic esters, entries 1-7, were converted to the desired allylated products in good yields. Substitution in the 2-position of the allyl group resulted in a lower yield (entry 8),



Entry	Substrate	Product	Yield (%)
1-7	<b>3.78, 3.80 - 3.85</b>	<b>3.102, 3.126 - 3.131</b>	R = CH <sub>2</sub> Ph, 79% R = Et, 76% R = Pr, 82% R = hexyl, 86% R = -(CH <sub>2</sub> ) <sub>6</sub> -, 65% R = allyl, 85% R = CH <sub>2</sub> CO <sub>2</sub> Et, 88%
8	<b>3.86</b>	<b>3.132</b>	69
9	<b>3.87</b>	<b>3.133</b>	77
10	<b>3.89</b>	<b>3.134</b>	51 (+16% protonated)
11	<b>3.88</b>	<b>3.135</b>	76
12	<b>3.94</b>	<b>3.136</b>	75
13	<b>3.91</b>	<b>3.137</b>	37
14	<b>3.100</b>	<b>3.138</b>	57
15	<b>3.98</b>	<b>3.139</b>	90
16	<b>3.101</b>	<b>3.140</b>	90
17	<b>3.99</b>	<b>3.141</b>	84

Figure 3.10. Substrate scope for BTMP sulfone DcA.

but was well-tolerated in the 3-position (entry 9) in the crotyl-based substrate. Likewise, the cinnamyl-based substrate (entry 11) resulted in a good yield. Substitution in the 1-position (entry 10) yielded the linear product as is typical in palladium-catalyzed allylation processes. The yield, however, was substantially lower than the crotyl analogue (77% vs 51%). Additionally, 16% protonated material was isolated in entry 10.

The compounds shown in Figure 3.11 were those that gave predominantly protonated product, and no observable allylated product. Substitution at the 1-position is minimally tolerated on otherwise unsubstituted allyls (as observed in the 1-methyl allyl example) but with lowered yield. The same substrate with a terminal phenyl group, however, gave no allylated product. A more sterically demanding mono substitution (cyclohexenyl) or disubstitution was not tolerated. Also, disubstitution in the terminal position was detrimental to the formation of the allylated product. It is interesting to note that monitoring the reaction by TLC

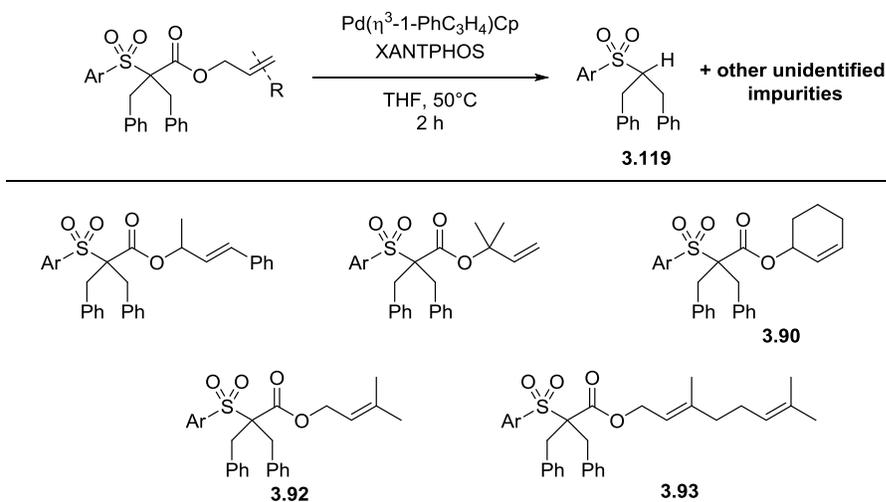


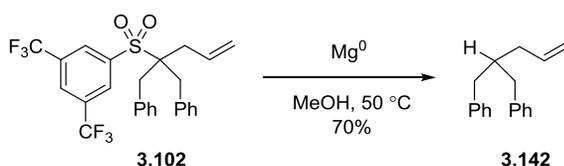
Figure 3.11. Substrates that yielded only protonated product.

showed that starting material persisted for ~ 80% of the reaction time, then it was consumed very rapidly to produce only protonated product.

It is important to note that even after the optimization work that was performed, and the relatively wide substrate scope that was established, the  $\alpha,\alpha$ -dimethyl substrate remained an enigma. Under the optimized conditions, only starting material was recovered, even upon extended heated at 50 °C. We were able to induce reactivity by heating at 65 °C for 5 hours, but substantial amounts of protonated, as well as allylated and cyclopropanated products were still formed. We elected to study this substrate more carefully and try to determine the origin of the protonated product. This is discussed extensively in Chapter 4.

### 3.11 Reductive Cleavage of Sulfones

To establish that the original goal of using DcA of sulfones as an alkane synthon, a homoallylic sulfone product from the DcA reaction was subjected to reductive conditions (magnesium metal in methanol at 50 °C) (Scheme 3.10). This same manipulation was used in Tunge and Weaver's work with phenyl sulfones.<sup>67</sup>



Scheme 3.10. Reductive cleavage of BTMP sulfone from homoallylic product.

### 3.12 Summary

Using BTMP sulfones as a triflone substitution, the substrate scope was explored. While the reactivity and selectivity is not as high as for the triflones, the BTMP sulfones are still quite reactive and selectivity can be tuned with reaction

temperature. The use of the pre-catalyst developed by Baird proved to be crucial for good reactivity and reproducibility. All types of  $\alpha,\alpha$ -disubstitution are tolerated (with the exception of  $\alpha,\alpha$ -dimethyl); the reaction is quite sensitive to substitution on the allyl group, however. The reaction is slowed substantially when there is substitution in the 1-position, and only protonated product is obtained when there is disubstitution in either the 1- or 3-position.

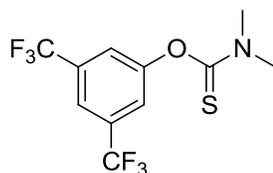
### 3.11 Experimental

#### General

All reagents were purchased from commercial sources and were used as received, without further purification, unless otherwise noted. DCM, toluene, Et<sub>2</sub>O, were distilled from CaH<sub>2</sub> immediately prior to use. DME, MTBE, MeCN and DMF were distilled from CaH<sub>2</sub> and stored over activated 4 Å molecular sieves under a nitrogen atmosphere. Tetrahydrofuran was distilled from lithium aluminum hydride or sodium/benzophenone prior to use. Reactions were monitored by thin-layer chromatography (TLC) using glass-backed extra hard layer (60 Å) TLC plates from Silicycle and visualized by fluorescence quenching under ultraviolet (UV) light and/or staining using potassium permanganate or ceric ammonium nitrate. Microwave heating was performed in glass vials (crimp-sealed with a septum liner and a metal fastener) in a Biotage Initiator 2.5 instrument with the absorption level set to “normal”. 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 Still *et al.*<sup>68</sup> or by automated chromatography on a Biotage Isolera One equipped with a UV detector. Concentration in vacuo refers to rotary evaporation with a 40°C water bath at the appropriate pressure for the given solvent. Yields refer to purified and spectroscopically pure compounds unless indicated as crude. NMR spectra were recorded on a Bruker Avance III 300 or Bruker AMX 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm). Spectra are referenced to the internal standard tetramethylsilane (TMS) (0.00 ppm). <sup>19</sup>F NMR spectra are referenced to trifluorotoluene (- 63.7 ppm). Infrared (IR) spectra were

recorded on a Varian 1000 Scimitar Series or an ABB Bomem MB series spectrometer. Absorptions are given in wavenumbers ( $\text{cm}^{-1}$ ). High resolution mass spectrometry (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV at the Ottawa-Carleton Mass Spectrometry Center or on a Bruker Maxis Impact Quadrupole-Time of Flight Mass Spectrometer in positive ESI mode at the McGill Chemistry Mass Spectrometry Center.

**O-(3,5-bis(trifluoromethyl)phenyl) dimethylcarbamothioate (3.3)**

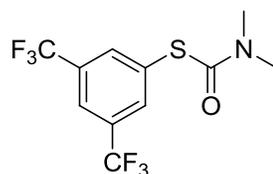


3,5-Bis(trifluoromethyl)phenol (10.0 g, 43.5 mmol, 1.0 equiv.) was added in portion to a solution of potassium hydroxide (2.56 g, 45.7 mmol, 1.05 equiv.) in distilled water (160 mL). This solution was stirred for 15 minutes at room temperature. *Note: depending on the quality of the phenol, there may be a dark brown oil that separates from the solution during this time. Experiments were performed in which the oil was separated and also in which the oil was left in the reaction mixture. There is negligible impact on yield and quality of final product.* A solution of N,N-dimethylthiocarbamoyl chloride (5.92 g, 47.9 mmol, 1.1 equiv) (STENCH WARNING!) in acetone (160 mL) was prepared. *Note: This reagent typically does not fully dissolve in acetone.* This solution was added in portions to the phenolate solution with vigorous stirring. The reaction mixture was allowed to stir for 6 h at

room temperature. *Note: Reaction may be left stirring overnight if desired.* The reaction mixture was cooled using an ice bath, and the pH was adjusted to 3 using 1 M HCl. The product was extracted using 3 x 200 mL EtOAc, then the combined organics were washed with 2 x 200 mL COLD water and 2 x 200 mL brine. *Note: The use of cold water is very helpful in preventing emulsions at this step.* The organic phase was dried with MgSO<sub>4</sub>, filtered and concentrated to produce an orange oil that solidified upon standing. The crude material was purified by passing through a silica plug. Hexane was used to elute the non-polar impurities, followed by 20% EtOAc/hexane to elute the product. Concentrated eluent gave 13.5 g (98%) yellow oil that solidified upon standing. Spectral data was in agreement with literature.<sup>75</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.76 (s, 1H), 7.55 (s, 2H), 3.47 (s, 3H), 3.38 (s, 3H).

**S-(3,5-bis(trifluoromethyl)phenyl) dimethylcarbamothioate (3.5)**



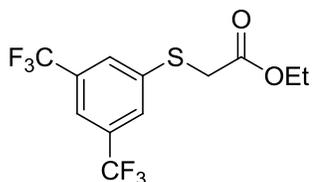
A round-bottom flask equipped with a magnetic stir bar was charged with **3.3** (25.5 g, 80.4 mmol, 1 equiv). (The flask should be approximately three-quarters full with the solid to minimize charring of product). The flask was immersed in a pre-heated oil bath, set to 225 °C. No stirring was used until most of the solid had melted. The flask was then flushed with argon or nitrogen, and an inert atmosphere was maintained during the reaction. The mixture darkened during the course of the reaction, typically yielding a dark brown liquid. The reaction mixture was stirred for

6 h, then a small sample was removed and analyzed by  $^1\text{H}$  NMR for completion. (Note: If reaction is not complete, return the flask to the oil bath. Continue to monitor by  $^1\text{H}$  NMR until complete. If necessary, an incomplete reaction may be left under inert atmosphere and then re-heated to continue reaction the next day.)

The material was purified by column chromatography, using 100% hexane initially to elute non-polar impurities, then using 10% EtOAc/hexane to elute product. Concentration of column fractions yielded a light yellow oil (21.9 g, 86%). Spectral data matched with literature data.<sup>75</sup>

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.97 (s, 2H), 7.28 (s, 1H), 3.06-3.15 (m, 6H)

**Ethyl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.7)**

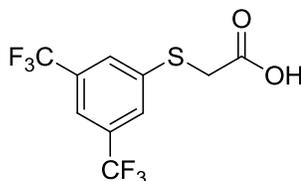


A solution of KOH (9.03 g, 161 mmol, 10 equiv) in water (120 mL) was added slowly to a solution of compound **3.5** (5.10 g, 16.1 mmol, 1.0 equiv) in methanol (480 mL). The reaction mixture was stirred overnight, then glacial acetic acid (8.3 mL, 145 mmol, 9.0 equiv) was added. This solution was stirred for 30 minutes, then ethyl chloroacetate (1.72 mL, 16.1 mmol, 1.0 equiv.) was added in one portion. Reaction was stirred at room temperature until reaction completion, as shown by TLC. Most of the solvent was removed via rotary evaporation, then the residue was extracted with EtOAc (2 x 200 mL). The combined extracts were washed with brine, dried over  $\text{MgSO}_4$ , then filtered and concentrated in vacuo. The

crude product was purified via column chromatography (5% EtOAc/hexane) to give 4.02 g (69%) of a pale yellow oil.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.81 (s, 2H), 7.70 (s, 1H), 4.21 (q, *J* = 7.3 Hz, 2H), 3.73 (s, 2H), 1.25 (t, *J* = 7.3 Hz, 3H).

**2-((3,5-bis(trifluoromethyl)phenyl)thio)acetic acid (3.13)**



Compound **3.7** (4.00 g, 11.0 mmol, 1 equiv.) was dissolved in THF (140 mL, 0.08 M), then 1 N NaOH<sub>(aq)</sub> (55 mL, 55.0 mmol, 5 equiv.). The reaction mixture was stirred vigorously until TLC showed all starting material had been consumed. The THF was removed *in vacuo*, then using 6 N HCl, the residue was adjusted from pH 14 to 3. The residue was extracted with 2 x 150 mL diethyl ether, then the combined extracts were washed with 2 x 100 mL brine. The organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give 3.34 g (quantitative yield) of a white, waxy solid (**3.13**).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400MHz): δ 10.89 (br s, 1H) 7.82 (s, 2H), 7.72 (s, 1H), 3.77 (s, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100MHz): δ 174.0, 138.2, 132.4 (q, *J* = 33 Hz), 128.9 (d, *J* = 3 Hz), 122.8 (q, *J* = 271 Hz), 120.7 (quintet, *J* = 4 Hz), 35.4.

**<sup>19</sup>F NMR** (376 MHz) δ -64.1 ppm.

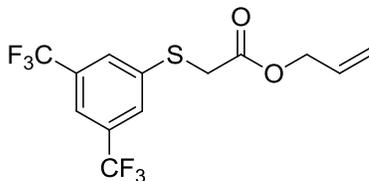
**IR** (film): 3089 (br), 2918, 2674, 2562, 1708, 1602, 1421, 1337, 1279, 1130.

**HRMS**: m/z calcd for C<sub>10</sub>H<sub>6</sub>O<sub>2</sub>F<sub>6</sub>S: 303.9993; Found: 303.9963.

### General Procedure for Esterification

A Biotage microwave vial was charged with a Teflon-coated stirbar and carboxylic acid (1.0 equiv). Methylene chloride (0.5 M relative to carboxylic acid) was added to dissolve and the vial was sealed with a crimp top lid equipped with a septum. In sequence, pivaloyl chloride (1.0 equiv), base (2.0 equiv) and alcohol (1.0 equiv) were added by syringe through the septum. In the case of solid bases or alcohols, the final sealing of the tube was delayed until addition was complete. The vial was heated for the indicated time at the indicated temperature in the microwave reactor. The reaction mixture was then diluted with diethyl ether, causing a white precipitate to form. This was washed with ice cold 0.1 M H<sub>2</sub>SO<sub>4</sub>. The layers were separated and the aqueous phase was extracted again with diethyl ether. The combined organic extracts were washed once with brine, then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was purified via flash chromatography using 5% EtOAc/hexanes.

### Allyl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.11)



**Reaction Time & Temperature:** 45 min, 80 °C

**Base:** Pyridine

**Yield:** 81%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.81 (s, 2H), 7.70 (s, 1H), 5.87 (ddt, 1H, *J* = 17.2, 10.4, 6.0 Hz), 5.31 (ddt, 1H, *J* = 17.1, 1.3, 1.2 Hz), 5.26 (ddt, 1H, *J* = 10.5, 1.3, 1.2 Hz), 4.63 (ddd, 1H, *J* = 6.0, 1.3, 1.2 Hz), 3.76 (s, 2H).

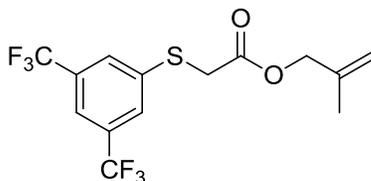
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.37, 138.8, 132.7 (q, *J* = 66 Hz), 131.1, 128.7 (d, *J* = 3 Hz), 122.9 (q, *J* = 271 Hz), 120.4 (quintet, *J* = 4 Hz), 119.5, 66.6, 35.6.

**<sup>19</sup>F NMR** (376 MHz) δ -64.1 ppm.

**IR** (film): 3090, 2951, 1740, 1459, 1414, 1355, 1278, 1183, 1135.

**HRMS:** *m/z* calcd for C<sub>13</sub>H<sub>10</sub>O<sub>2</sub>F<sub>6</sub>S: 344.0306; Found: 344.0320.

**2-Methylallyl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.36)**



**Reaction Time & Temperature:** 90 min, 80 °C

**Base:** Pyridine

**Yield:** 80%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.81 (s, 2H), 7.70 (s, 1H), 4.95 (m, 1H), 4.94 (m, 1H), 4.55 (s, 1H), 3.78 (s, 1H), 1.71 (s, 3H).

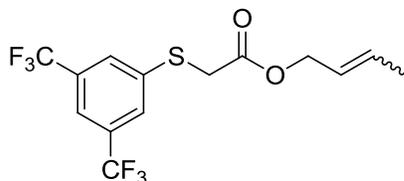
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.4, 139.0, 138.9, 132.4 (q, *J* = 66 Hz), 128.6 (d, *J* = 4 Hz), 123.0 (q, *J* = 271 Hz), 120.4 (quintet, *J* = 4 Hz), 114.1, 69.3, 35.7, 19.4.

**<sup>19</sup>F NMR** (376 MHz) δ -64.1 ppm.

**IR** (film) 3087, 2981, 2945, 1739, 1455, 1355, 1278, 1184, 1137.

**HRMS:** m/z calcd for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>F<sub>6</sub>S: 358.0462; Found: 358.0454.

**But-2-en-1-yl-2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.37)**



**Reaction Time & Temperature:** 45 min, 80 °C

**Base:** Pyridine

**Yield:** 75%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz) (mixture of cis/trans isomers): δ 7.80 (s, 2H), 7.69 (s, 1H), 5.76-5.84 (m, 1H), 5.49-5.57 (m, 1H), 4.70 (d, *J* = 7 Hz, minor isomer, integration 0.13, 2H), 4.56 (d, *J* = 6.5 Hz, major isomer, integration 2.00, 2H), 3.74 (s, minor isomer, integration 0.19, 2H), 3.73 (s, major isomer, integration 1.99, 2H), 1.68-1.71 (m, minor & major isomers; overlapping -CH<sub>3</sub> peak, 3H)

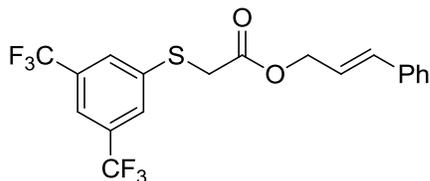
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz)(mixture of cis/trans isomers): δ 168.6, 139.1, 132.9, 132.4 (q, *J* = 66Hz), 131.0 (minor isomer), 128.7 (d, *J* = 3 Hz), 124.2, 123.2 (minor isomer), 123.1 (q, *J* = 271 Hz), 120.3 (quintet, *J* = 4 Hz), 66.8, 61.6 (minor isomer), 35.7, 26.6 (minor isomer), 17.7, 13.1 (minor isomer).

**<sup>19</sup>F NMR** (376 MHz) δ -64.2 ppm.

**IR** (film): 3461, 3085, 3029, 2950, 2924, 2889, 1739, 1678, 1602, 1452, 1412, 1354, 1279, 1184, 1132.

**HRMS:** m/z calcd for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>F<sub>6</sub>S: 358.0462; Found: 358.0482.

**Cinnamyl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.38)**



**Reaction Time & Temperature:** 120 min, 80 °C

**Base:** Pyridine

**Yield:** 76%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.82 (s, 2H), 7.67 (s, 1H), 7.28-7.37 (m, 5H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.22 (dt, *J* = 16.0, 6.8 Hz, 1H), 4.79 (dd, *J* = 6.4, 0.8 Hz, 2H), 3.78 (s, 1H).

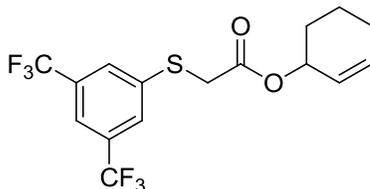
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.5, 135.8, 135.5, 132.3 (q, *J* = 66 Hz), 128.7, 128.5 (d, *J* = 4 Hz), 128.4, 126.7, 123.0 (q, *J* = 237 Hz), 121.8, 120.3 (quintet, *J* = 4 Hz), 66.6, 35.6.

**<sup>19</sup>F NMR** (376 MHz): δ -64.0.

**IR** (film): 3226, 3085, 3029, 2962, 1737, 1495, 1450, 1354, 1277, 1133.

**HRMS:** *m/z* calcd for C<sub>19</sub>H<sub>14</sub>O<sub>2</sub>F<sub>6</sub>S: 420.0619; Found: 420.0611.

**Cyclohex-2-en-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.39)**



**Reaction Time & Temperature:** 120 min, 80 °C

**Base:** Pyridine

**Yield:** 78%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.80 (s, 2H), 7.69 (s, 1H), 5.94-5.99 (m, 1H), 5.62-5.67 (m, 1H), 5.28-5.29 (m, 1H), 3.73 (s, 2H), 1.94-2.10 (m, 2H), 1.79-1.86 (m, 1H), 1.58-1.73 (m, 3H).

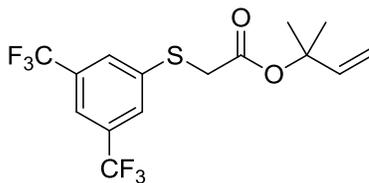
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.3, 139.2, 133.8, 132.3 (q, *J* = 67 Hz), 128.5 (d, *J* = 4 Hz), 124.5, 123.0 (q, *J* = 272 Hz), 120.2 (quintet, *J* = 4 Hz), 70.0, 35.9, 28.1, 24.8, 18.5.

**<sup>19</sup>F NMR** (376 MHz): δ -64.1.

**IR** (film): 3094, 3038, 2945, 2872, 2839, 1733, 1617, 1602, 1457, 1397, 1355, 1279, 1183, 1136, 1050, 1009.

**HRMS:** *m/z* calcd for C<sub>16</sub>H<sub>14</sub>F<sub>6</sub>O<sub>2</sub>S: 384.0619; Found: 384.0609.

**2-Methylbut-3-en-2-yl-2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.40)**



**Reaction Time & Temperature:** 120 min, 80 °C

**Base:** Pyridine

**Yield:** 73%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.78 (s, 2H), 7.68 (s, 1H), 6.02 (dd, 1H, 17.4, 10.9 Hz), 5.17 (d, 1H, 17.5 Hz), 5.09 (d, 1H, 10.8 Hz), 3.67 (s, 3H), 1.49 (s, 6H).

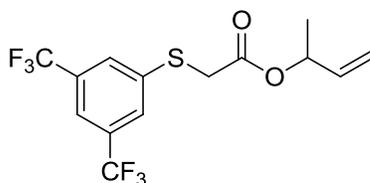
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 167.3, 141.3, 139.4, 132.3 (q, *J* = 66 Hz), 128.3 (d, *J* = 3 Hz), 123.0 (q, *J* = 271 Hz), 120.0 (quintet, *J* = 4 Hz), 113.7, 83.1, 36.5, 26.2.

**<sup>19</sup>F NMR** (376 MHz): δ -64.1.

**IR** (film): 3093, 2987, 2930, 1733, 1460, 1414, 1355, 1279, 1186, 1142.

**HRMS**: *m/z* calcd for C<sub>15</sub>H<sub>14</sub>F<sub>6</sub>O<sub>2</sub>S: 372.0619; Found: 372.0634.

**But-3-en-2-yl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.41)**



**Reaction Time & Temperature**: 120 min, 80 °C

**Base**: Pyridine

**Yield**: 65%.

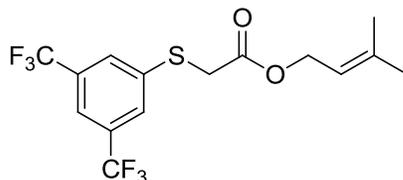
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.80 (s, 2H), 7.69 (s, 1H), 5.77 (ddd, *J* = 16.8, 10.4, 6.0 Hz, 1H), 5.37 (dq, *J* = 6.4, 6.4 Hz, 1H), 5.23 (d, *J* = 16.8 Hz, 1H, additional fine coupling), 5.15 (d, *J* = 10.8 Hz, 1H, additional fine coupling), 3.73 (s, 2H), 1.30 (d, *J* = 6.4 Hz, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.9, 139.0, 136.6, 132.2 (q, *J* = 34 Hz), 128.5 (d, *J* = 3 Hz), 122.9 (q, *J* = 271 Hz), 120.1 (quintet, *J* = 4 Hz), 116.9, 73.1, 35.7, 19.6.

**<sup>19</sup>F NMR** (376 MHz): δ -64.0.

**IR** (film): 3091, 2988, 2937, 1735, 1648, 1618, 1457, 1414, 1355, 1287, 1187, 1044.

**3-Methylbut-2-en-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.44)**



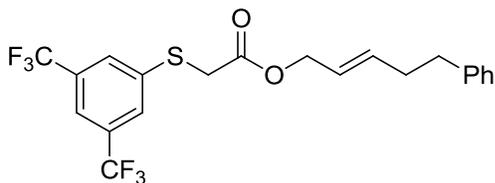
**Reaction Time & Temperature:** 90 min, 80 °C

**Base:** Pyridine

**Yield:** 70%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.80 (s, 2H), 7.69 (s, 1H), 5.29 (tq, *J* = 7.6, 1.6 Hz, 1H), 4.63 (d, *J* = 7.6 Hz, 2H), 3.73 (s, 2H), 1.74 (s, 3H), 1.68 (s, 3H).

**(E)-5-phenylpent-2-en-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.43)**



**Reaction Time & Temperature:** 90 min, 80 °C

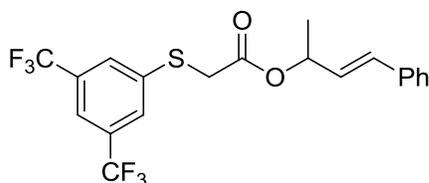
**Base:** Pyridine

**Yield:** 63% (reasonably pure – troublesome impurities were more conveniently removed at a later step. The NMR data given below is for the major product)

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.82 (s, 2H), 7.71 (s, 1H), 7.30 – 7.32 (m, 2H), 7.17 – 7.23 (m, 3H), 5.81 – 5.88 (m, 1H), 5.54 – 5.61 (m, 1H), 4.59 (d, *J* = 6.4 Hz, 2H), 3.75 (s, 2H), 2.68 – 2.72 (m, 2H), 2.36 – 2.41 (m, 2H). 45

**(*E*)-4-phenylbut-3-en-2-yl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate**

**(3.42)**



**Reaction Time & Temperature:** 120 min, 80 °C

**Base:** Pyridine

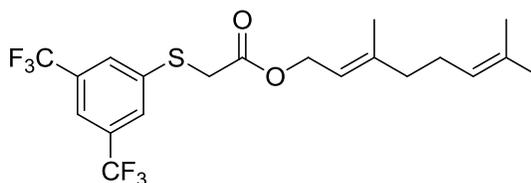
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.81 (s, 2H), 7.65 (s, 1H), 7.29 -7.32 (m, 5H), 6.59 (d, *J* = 16.0 Hz, 1H), 5.55 (dq, *J* = 6.4, 6.4 Hz, 1H), 3.75 (s, 2H), 1.39 (d, *J* = 6.4 Hz, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.9, 139.0, 135.9, 132.7, 132.2 (q, *J* = 33 Hz), 128.6, 128.3 (unresolved fine coupling), 128.2, 127.5, 126.6, 122.9 (q, *J* = 271 Hz), 120.1 (unresolved fine coupling), 73.3, 35.7, 20.1.

**<sup>19</sup>F NMR** (376 MHz): δ -64.0.

**IR** (film): 3032, 2985, 2935, 1735, 1355, 1279, 1183, 1136, 1037.

**(*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-((3,5-bis(trifluoromethyl) phenyl)thio)acetate (3.45)**



**Reaction Time & Temperature:** 90 min, 80 °C

**Base:** Pyridine

**Yield:** 74%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.80 (s, 2H), 7.69 (s, 1H), 5.28 – 5.31 (m, 1H), 5.05 – 5.06 (m, 1H), 4.66 (d, *J* = 7.2 Hz, 2H), 3.74 (s, 2H), 2.03 – 2.08 (m, 4H), 1.68 (s, 6H), 1.59 (s, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 168.7, 143.7, 139.1, 132.2 (q, *J* = 33 Hz), 131.9, 128.3 (unresolved fine coupling), 123.6, 122.9 (q, *J* = 271 Hz), 120.1 (quintet, *J* = 3 Hz), 117.2, 62.9, 39.5, 35.6, 26.2, 25.6, 17.6, 16.4.

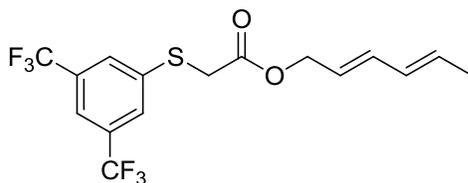
**<sup>19</sup>F NMR** (376 MHz): δ -64.0.

**IR** (film): 3085, 2970, 2859, 1738, 1355, 1278, 1183, 1137.

**HRMS:** *m/z* calcd for C<sub>20</sub>H<sub>22</sub>F<sub>6</sub>NaO<sub>2</sub>S: 463.1142; Found: 463.1134.

**(2*E*,4*E*)-hexa-2,4-dien-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate**

**(3.46)**



**Reaction Time & Temperature:** 90 min, 80 °C

**Base:** Pyridine

**Yield:** 68%.

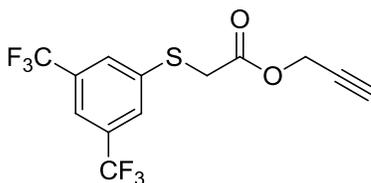
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.80 (s, 2H), 7.69 (s, 1H), 6.20 – 6.27 (m, 1H), 5.98 – 6.04 (m, 1H), 5.71 – 5.80 (m, 1H), 5.51 – 5.58 (m, 1H), 4.62 (d, *J* = 7.2 Hz, 2H), 3.74 (s, 2H), 1.77 (d, *J* = 6.4 Hz, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 168.4, 138.9, 136.2, 132.2 (q, *J* = 33 Hz), 132.1, 130.1, 128.6 (d, *J* = 2 Hz), 122.9 (q, *J* = 271 Hz), 122.3, 120.2 (quintet, *J* = 3 Hz), 66.5, 35.6, 18.1.

**<sup>19</sup>F NMR** (376 MHz): δ – 64.0.

**IR** (film): 3027, 2941, 1736, 1662, 1617, 1448, 1355, 1278, 1183, 1136.

**Prop-2-yn-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.47)**



**Reaction Time & Temperature:** 45 min, 80°C

**Base:** Pyridine

**Yield:** 74%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.83 (s, 2H), 7.72 (s, 1H), 4.73 (d, 2H, *J* = 2.8 Hz), 3.77 (s, 2H), 2.48 (t, *J* = 2.4 Hz, 1H).

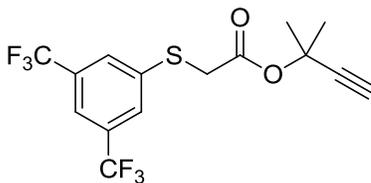
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.0, 138.4, 132.4 (q, *J* = 33 Hz), 129.1 (d, *J* = 3 Hz), 122.9 (q, *J* = 272 Hz), 120.6 (quintet, *J* = 4 Hz), 76.6, 75.7, 53.3, 35.5.

**<sup>19</sup>F NMR** (376 MHz): δ -64.1.

**IR** (film): 3310, 3087, 2954, 2917, 2849, 2257, 2134, 1747, 1618, 1438, 1355, 1279, 1185, 1139, 1025.

**HRMS:** *m/z* calcd for C<sub>13</sub>H<sub>8</sub>F<sub>6</sub>O<sub>2</sub>S: 342.0149; Found: 342.0169.

**2-Methylbut-3-yn-2-yl-2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.48)**



**Reaction Time & Temperature:** 180 min, 80 °C

**Base:** Pyridine

**Yield:** 56%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.81 (s, 2H), 7.70 (s, 1H), 3.69 (s, 2H), 2.53 (s, 1H), 1.64 (s, 3H).

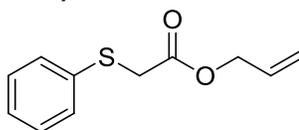
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 166.9, 139.0, 132.3 (q, *J* = 33 Hz), 128.7 (d, *J* = 4 Hz), 123.0 (q, *J* = 271 Hz), 120.2 (quintet, *J* = 4 Hz), 83.6, 73.8, 73.2, 36.3, 28.6.

**<sup>19</sup>F NMR** (376 MHz): δ - 64.0.

**IR** (film): 3312, 2997, 2994, 1744, 1386, 1355, 1279, 1185, 1136.

**HRMS:** *m/z* calcd for C<sub>15</sub>H<sub>12</sub>F<sub>6</sub>O<sub>2</sub>S: 370.0462; Found: 370.0454.

**Allyl 2-(phenylthio)acetate (3.53)**



**Reaction Time & Temperature:** 90 min, 80 °C

**Base:** Pyridine

**Yield:** 76%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.40-7.43 (m, 2H), 7.28-7.32 (m, 2H), 7.21-7.25 (m, 1H), 5.86 (ddt, *J* = 17.2, 10.8, 5.6 Hz, 1H), 5.29 (ddt, *J* = 17.2, 1.6, 1.2 Hz, 1H),

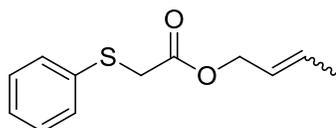
5.22 (ddt,  $J = 10.4, 1.2, 1.2$  Hz, 1H), 4.61 (ddd,  $J = 6.0, 1.2, 1.2$  Hz, 1H), 3.67 (s, 2H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz): 169.4, 134.9, 131.6, 130.1, 129.1, 127.0, 118.7, 66.1, 36.7.

**IR** (film): 3079, 3063, 3022, 2949, 1735, 1649, 1584, 1482, 1440, 1412, 1361, 1278.

**HRMS**:  $m/z$  calcd for  $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$ : 208.0558; Found: 208.0554.

**But-2-en-1-yl 2-(phenylthio)acetate (3.54)**



**Reaction Time & Temperature**: 90 min, 80 °C

**Base**: Pyridine

**Yield**: 73%.

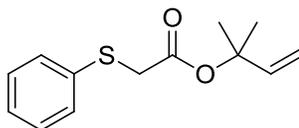
$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  7.39-7.43 (m, 2H) 7.29-7.33 (m, 2H), 7.20-7.28 (m, 1H), 5.71-5.83 (m, 1H), 5.47-5.58 (m, 1H), 4.66-4.68 (m, 1H, cis isomer), 4.52-4.55 (m, 1H, trans isomer), 3.65 (s, 2H), 1.67-1.72 (m, 3H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz): 169.5, 134.9, 132.0, 130.0, 129.0, 127.0, 124.5, 66.2, 36.7, 17.8.

**IR** (film): 3058, 3022, 2943, 2918, 1734, 1677, 1583, 1482, 1439, 1409, 1376, 1269, 1131, 1088, 1025.

**HRMS**:  $m/z$  calcd for  $\text{C}_{12}\text{H}_{14}\text{O}_2\text{S}$ : 222.0715; Found: 222.0719.

**2-Methylbut-3-en-2-yl 2-(phenylthio)acetate (3.55)**



**Reaction Time & Temperature:** 120 min, 80 °C

**Base:** Pyridine

**Yield:** 50%.

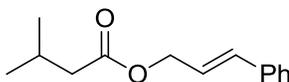
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.39-7.43 (m, 2H), 7.26-7.32 (m, 2H), 7.19-7.24 (m, 1H), 6.00 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.14 (d, *J* = 17.4 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 3.58 (s, 2H), 1.47 (s, 6H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 168.4, 141.8, 135.2, 129.9, 128.9, 126.8, 113.1, 82.1, 37.5, 26.2.

**IR** (film): 3061, 2982, 2935, 1863, 1808, 1732, 1645, 1584, 1482, 1440, 1413, 1285, 1238, 1184, 1119, 1027.

**HRMS:** *m/z* calcd C<sub>13</sub>H<sub>16</sub>O<sub>2</sub>S: 236.0871; Found: 236.0868.

**Cinnamyl 3-methylbutanoate (3.56)**



**Reaction Time & Temperature:** 45 min, 100 °C

**Base:** DMAP

**Yield:** 75%.

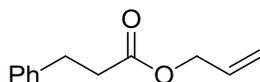
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.24-7.40 (m, 5H), 6.65 (d, 1H, *J* = 15.6 Hz), 6.29 (dt, 1H, *J* = 16, 6.4 Hz), 4.74 (dd, 2H, *J* = 6.4, 1.2 Hz), 2.24 (d, 2H, *J* = 6.8 Hz), 2.08-2.20 (m, 1H), 0.97 (d, 6H, *J* = 6.8 Hz).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 172.9, 136.3, 134.0, 128.6, 128.0, 126.6, 123.4, 64.8, 43.4, 25.7, 22.4.

**IR** (film): 3220, 3061, 3028, 2960, 2873, 1659, 1736, 1495, 1467, 1450, 1379, 1370, 1357, 1295, 1255, 1185, 1168, 1119, 1098.

**HRMS**: *m/z* calcd for C<sub>14</sub>H<sub>18</sub>O<sub>2</sub>: 218.1307; Found: 218.1305.

### Allyl 3-phenylpropanoate (3.58)



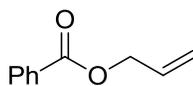
**Reaction Time & Temperature**: 45 min, 100 °C

**Base**: DMAP

**Yield**: 76%.

Spectral data matched literature.<sup>104</sup>

### Allyl benzoate (3.61)



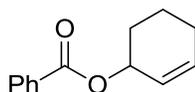
**Reaction Time & Temperature**: 45 min, 80 °C

**Base**: DMAP

**Yield**: 62%.

Spectral data matched literature.<sup>104</sup>

**Cyclohex-2-en-1-yl benzoate (3.62)**



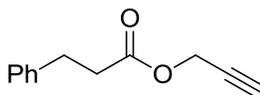
**Reaction Time & Temperature:** 45 min, 80 °C

**Base:** DMAP

**Yield:** 66%.

Spectral data matched literature.<sup>105</sup>

**Prop-2-yn-1-yl 3-phenylpropanoate (3.59)**

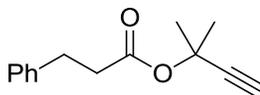


**Reaction Time & Temperature:** 90 min, 100 °C

**Yield** 71%.

Spectral data matched literature.<sup>106</sup>

**2-Methylbut-3-yn-2-yl 3-phenylpropanoate (3.60)**



**Reaction Time & Temperature:** 180 min, 100 °C

**Base:** DMAP

**Yield:** 68%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.26-7.30 (m, 2H), 7.18-7.21 (m, 3H), 2.97 (t, 2H, *J* = 8 Hz), 2.61 (t, 2H, *J* = 5 Hz), 2.53 (s, 1H).

**$^{13}\text{C}$  NMR** ( $\text{CDCl}_3$ , 100 MHz): 171.2, 140.5, 128.4, 128.3, 126.2, 84.7, 72.3, 71.7, 36.5, 30.9, 28.9.

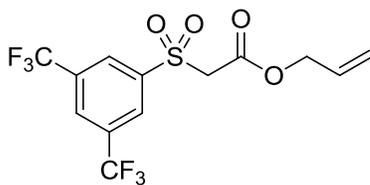
**IR** ( $\text{cm}^{-1}$ ): 3288, 3029, 2989, 2939, 2121, 1950, 1743, 1604, 1497, 1454, 1365, 1237, 1192, 1127, 1078.

**HRMS**:  $m/z$  calcd for  $\text{C}_{14}\text{H}_{16}\text{O}_2$ : 216.1150; Found: 216.1163.

### General Procedure for Oxidation

Starting sulfide (1 equiv.) was dissolved in tert-butanol (0.4 M relative to sulfide), then ammonium sulfate tetrahydrate (0.1 equiv.) was added. Hydrogen peroxide (35% in water, 4 equiv) was added via syringe. The reaction mixture turned bright yellow. The reaction was stirred at room temperature until completion, as shown by TLC. The solvent was evaporated *in vacuo*, then the residue was partitioned in an equal volume of sat.  $\text{NaHCO}_3(\text{aq})$  and EtOAc. The layers were separated, then the aqueous phase was extracted twice with EtOAc. The combined organic extracts were washed once with brine, then dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to yield a colorless or light yellow oil. Most substrates solidified to a waxy, off-white solid upon standing. Typically, the purity after this step was exceptionally high and the compounds were used without further purification.

### Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.65)



**Yield:** 86%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.42 (s, 2H), 8.19 (s, 1H), 5.83 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.31 (2 overlapping dd, 2H), 4.61 (d, *J* = 6.0 Hz, 2H – some fine splitting observed), 4.24 (s, 2H).

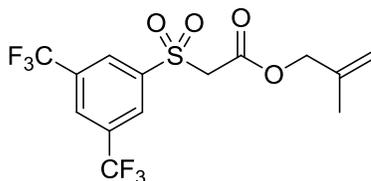
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 161.5, 141.3, 133.1 (q, *J* = 34 Hz), 130.3, 129.4 (unresolved fine splitting), 128.0 (quintet, *J* = 3 Hz), 122.3 (q, *J* = 272 Hz), 120.4, 67.3, 60.6.

**<sup>19</sup>F NMR** (376.5 MHz): δ -63.9.

**IR** (film): 3086, 2950, 1740, 1361, 1283, 1151.

**HRMS:** *m/z* calcd for C<sub>13</sub>H<sub>10</sub>F<sub>6</sub>NaO<sub>4</sub>S: 399.0102; Found: 399.0091.

**2-Methylallyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.66)**



**Yield:** 99%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.42 (s, 2H), 8.18 (s, 1H), 4.96 (m, 1H), 4.95 (m, 1H), 4.53 (s, 2H), 4.25 (s, 2H), 1.71 (s, 3H).

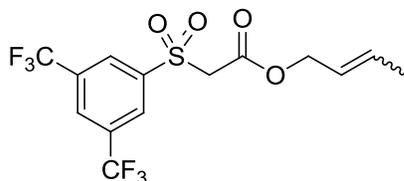
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 161.5, 141.3, 138.3, 133.2 (q, *J* = 35 Hz), 129.4 (d, *J* = 4 Hz), 128.0 (unresolved mult), 122.3 (q, *J* = 272 Hz), 114.9, 70.0, 60.6, 19.3.

**<sup>19</sup>F NMR** (376.5 MHz): δ -63.9.

**IR** (film): 3088, 2949, 1731, 1362, 1189, 1152, 1129, 1101.

**HRMS:** m/z calcd for C<sub>14</sub>H<sub>12</sub>F<sub>6</sub>NaO<sub>4</sub>S: 413.0258; Found: 413.0238.

**But-2-en-1-yl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.67)**



**Yield:** 85%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.42 (s, 2H), 8.19 (s, 1H), 5.81 (m, 1H), 5.49 (dtq, *J* = 15.2, 6.8, 1.6 Hz, 1H), 4.68 (d, *J* = 7.2 Hz, 2H, cis isomer, 6%), 4.56 (d, *J* = 6.8 Hz, 2H trans isomer, 94%), 4.21 (s, 2H), 1.72 (dm, *J* = 6.4 Hz, unresolved fine coupling, 3H, trans isomer), 1.68 (m, 3H, cis isomer).

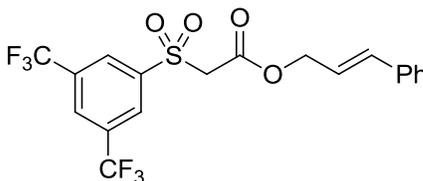
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 161.5, 141.3, 133.1 (q, *J* = 34 Hz), 129.4 (d, *J* = 3 Hz), 127.8 (unresolved mult), 122.3 (q, *J* = 272 Hz), 123.2, 67.5, 60.6, 17.7.

**<sup>19</sup>F NMR** (376.5 MHz): δ -63.9.

**IR** (film): 3088, 3012, 2951, 1731, 1396, 1363, 1285, 1285, 1153, 1127, 1101.

**HRMS:** m/z calcd for C<sub>14</sub>H<sub>12</sub>F<sub>6</sub>NaO<sub>4</sub>S: 413.0258; Found: 413.0246.

**Cinnamyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.68)**



**Yield:** 80%.

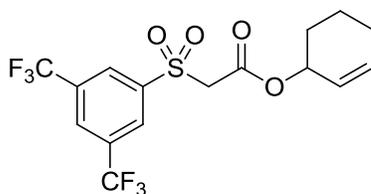
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.43 (s, 2H), 8.15 (s, 1H), 7.29-7.38 (mult, 5H), 6.64 (d, *J* = 16.0 Hz, some broadening of peaks, 1H), 6.16 (dt, *J* = 16.0, 6.8 Hz, 1H), 4.77 (dd, *J* = 6.4, 0.8 Hz, 2H), 4.25 (s, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 161.6, 141.3, 136.2, 135.5, 133.6 (q, *J* = 34 Hz), 129.4 (d, *J* = 4 Hz), 128.7, 128.6, 127.9 (unresolved mult), 126.7, 122.3 (q, *J* = 272 Hz), 120.8, 67.3, 60.5.

**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**IR** (film): 3088, 3029, 2996, 2940, 1738, 1364, 1337, 1315, 1279, 1156, 1137, 1102. **HRMS**: *m/z* calcd for C<sub>19</sub>H<sub>14</sub>F<sub>6</sub>NaO<sub>4</sub>S: 475.0415; Found: 475.0406.

**Cyclohex-2-en-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.70)**



**Yield**: 71%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.42 (s, 2H), 8.18 (s, 1H), 5.97 – 5.99 (m, 1H), 5.57 – 5.59 (m, 1H), 5.25 (br s, 1H), 4.22 (s, 2H), 1.94 – 2.08 (m, 2H), 1.77 – 1.84 (m, 1H), 1.58 – 1.69 (m, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 161.4, 141.5, 134.4, 133.1 (q, *J* = 35 Hz), 129.3 (d, *J* = 3 Hz), 127.8 (quintet, *J* = 3 Hz), 123.7, 122.3 (q, *J* = 272 Hz), 71.1, 60.8, 27.8, 24.6, 18.3.

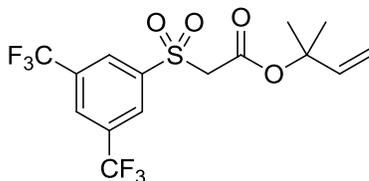
**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**IR** (film): 3089, 2945, 1737, 1360, 1348, 1281, 1186, 1151, 1104, 1050, 1007.

**HRMS**: *m/z* calcd for C<sub>16</sub>H<sub>14</sub>F<sub>6</sub>NaO<sub>4</sub>S: 439.0415; Found: 439.0416.

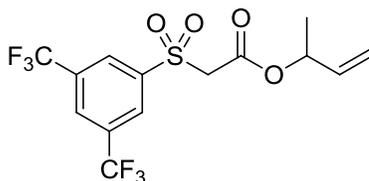
**2-Methylbut-3-en-2-yl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate**

**(3.71)**



Impurities present from esterification were still present. The crude material was carried through to the alkylation step.

**But-3-en-2-yl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.69)**



**Yield:** 94%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.41 (s, 2H), 8.18 (s, 1H), 5.73 (ddq, *J* = 6.4, 10.4, 17.2 Hz, 1H), 5.33 (dt, *J* = 6.4, 6.4 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.21 (s, 2H), 1.29 (d, *J* = 6.4 Hz, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 161.0, 141.3, 135.9, 133.1 (q, *J* = 34 Hz), 129.4 (d, *J* = 4 Hz), 127.9 (quintet, *J* = 4 Hz), 122.3 (q, *J* = 272 Hz), 117.7, 74.3, 60.9, 19.5.

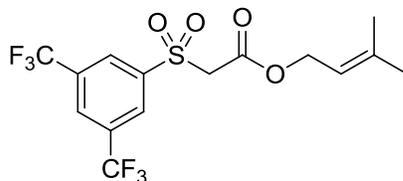
**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**IR** (film): 3083, 3012, 2952, 1729, 1363, 1283, 1151, 1135, 1100.

**HRMS:** *m/z* calcd for C<sub>14</sub>H<sub>12</sub>F<sub>6</sub>NaO<sub>4</sub>S: 413.0258; Found: 413.0248.

**3-Methylbut-2-en-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate**

**(3.74)**



**Yield:** 96%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.42 (s, 2H), 8.18 (s, 1H), 5.23 (m, 1H), 4.61 (d, *J* = 7.6 Hz), 4.21 (s, 2H), 1.75 (s, 3H), 1.68 (s, 3H).

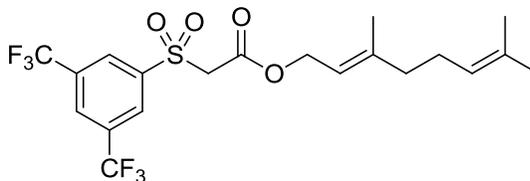
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 161.8, 141.4, 133.2 (q, *J* = 34 Hz), 129.4 (d, *J* = 4 Hz), 127.9 (quintet, *J* = 4 Hz), 122.3 (q, *J* = 272 Hz), 116.7, 63.6, 60.6, 25.7, 18.0.

**<sup>19</sup>F NMR** (376 MHz): δ - 63.9.

**IR** (film): 3091, 3013, 2982, 2952, 1730, 1400, 1362, 1338, 1283, 1188, 1152, 1130, 1101.

**HRMS:** *m/z* calcd for C<sub>15</sub>H<sub>14</sub>F<sub>6</sub>NaO<sub>4</sub>S: 427.0415; Found: 427.0411.

**(*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-((3,5-bis (trifluoromethyl) phenyl) sulfonyl) acetate (3.75)**



**Yield:** 22%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.42 (s, 2H), 8.18 (s, 1H), 5.22 – 5.26 (m, 1H), 5.06 (app br s, unresolved fine coupling, 1H), 4.64 (d, *J* = 7.2 Hz, 2H), 4.21 (s, 2H), 2.04 – 2.08 (m, 4H), 1.67 (s, 6H), 1.59 (s, 3H).

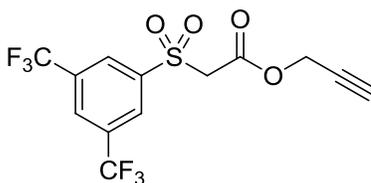
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 161.8, 144.6, 141.4, 133.0 (q, *J* = 35 Hz), 129.4 (d, *J* = 3 Hz), 127.8 (quintet, *J* = 3 Hz), 123.4, 122.3 (q, *J* = 272 Hz), 116.4, 63.6, 60.6, 39.5, 26.2, 25.6, 17.6, 16.4.

**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**IR** (film): 3086, 2972, 2930, 2859, 1741, 1360, 1347, 1280, 1186, 1149, 1101, 1049.

**HRMS**: *m/z* calcd for C<sub>20</sub>H<sub>22</sub>F<sub>6</sub>NaO<sub>4</sub>S: 495.1041; Found: 495.1050.

**Prop-2-yn-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.77)**



**Yield**: 92%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.44 (s, 2H), 8.20 (s, 1H), 4.72 (d, *J* = 2.4 Hz, 2H), 4.27 (s, 2H), 2.52 (t, *J* = 2.4 Hz, 1H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 161.1, 141.1, 133.2 (q, *J* = 35 Hz), 129.4 (d, *J* = 4 Hz), 128.1 (quintet, *J* = 4 Hz), 122.3 (q, *J* = 272 Hz), 76.4, 75.6, 60.3, 53.9.

**<sup>19</sup>F NMR** (376 MHz): δ -63.8.

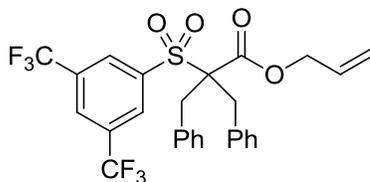
**IR** (film): 3296, 3256, 3091, 3003, 2942, 2133, 1752, 1361, 1341, 1280, 1143, 1102, 1014.

**HRMS**: *m/z* calcd for C<sub>13</sub>H<sub>8</sub>F<sub>6</sub>NaO<sub>4</sub>S: 396.9945; Found: 396.9927.

## General Procedure for $\alpha,\alpha$ -Dialkylation of Sulfones

An oven-dried round-bottom flask was charged with the appropriate sulfone (1 equiv). Under an inert atmosphere, dry DMF (0.1 M relative to sulfone) was added via syringe. Finely powdered anhydrous  $K_2CO_3$  (5 equiv) was added to the reaction mixture in a single portion. The reaction mixture was allowed to stir for 15 minutes at room temperature. Typically, the reaction mixture turned yellow in color during this time. All alkyl halides were purified immediately prior to use by passage through a short column of activated basic alumina in a Pasteur pipet fitted with a cotton plug. Purified alkyl halide (5 equiv, if volatile; 2.3 equiv, if not) was added via syringe to flask. The reaction mixture stirred at room temperature until deemed complete by TLC. The reaction mixture was diluted with water (5x volume of DMF), then extracted five times with EtOAc. The combined organic extracts were washed once with water, once with brine, then dried over  $MgSO_4$ , filtered and concentrated *in vacuo*. The material was purified by flash chromatography (typically 5% EtOAc/hexane) to give product.

### Allyl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.78)



**Yield:** 98%.

**$^1H$  NMR** ( $CDCl_3$ , 400 MHz):  $\delta$  8.16 (s, 2H), 8.02 (s, 1H), 7.21 – 7.22 (m, 10H), 5.81 (ddt,  $J$  = 17.2, 10.8, 6.0 Hz, 1H), 5.34 (br s, 1H), 5.28 – 5.30 (m, 1H), 4.62 (d,  $J$  = 6.0 Hz, 2H), 3.52 (d,  $J$  = 14.0 Hz, 2H), 3.44 (d,  $J$  = 14.0 Hz, 2H).

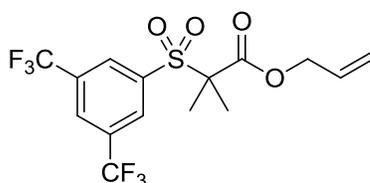
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.1, 141.4, 133.7, 132.1 (q, *J* = 34 Hz), 131.04 (d, *J* = 4 Hz), 130.95, 130.0, 122.4 (q, *J* = 271 Hz), 120.7, 79.4, 67.2, 39.6.

**<sup>19</sup>F NMR** (376.5 MHz): δ – 63.6.

**IR** (film): 3091, 3070, 3035, 2936, 1738, 1650, 1625, 1603, 1497, 1456, 1427, 1357, 1334, 1280, 1186, 1145, 1098, 1032.

**HRMS**: *m/z* calcd for C<sub>27</sub>H<sub>22</sub>F<sub>6</sub>NaO<sub>4</sub>S: 579.1041; Found: 579.1054.

**Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-methylpropanoate (3.79)**



**Yield**: 95%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.32 (s, 2H), 8.18 (s, 1H), 5.86 (ddt, *J* = 16.3, 10.5, 5.9 Hz, 1H), 5.39 – 5.26 (m, 2H), 4.62 (dt, *J* = 5.9, 1.3 Hz, 2H), 1.69 (s, 6H).

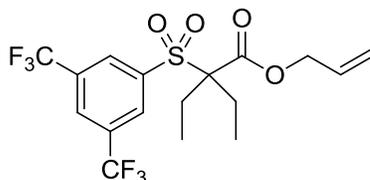
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 168.0, 138.7, 132.5 (q, *J* = 35 Hz), 130.9 (d, *J* = 3 Hz), 130.4, 127.7 (quintet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.9, 69.9, 67.1, 20.0.

**<sup>19</sup>F NMR** (376.5 MHz): δ – 63.8.

**IR** (film): 3090, 2995, 2950, 1745, 1651, 1626, 1606, 1470, 1393, 1360, 1334, 1316, 1281, 1181, 1137, 1097.

**HRMS**: *m/z* calcd for C<sub>15</sub>H<sub>14</sub>F<sub>6</sub>NaO<sub>4</sub>S: 427.0415; Found: 427.0418.

**Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-ethylbutanoate (3.80)**



**Yield**: 92%.

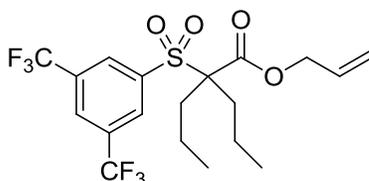
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.29 (s, 2H), 8.15 (s, 1H), 5.83 (ddt, *J* = 17.2, 10.8, 6.0 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.58 (d, *J* = 6.0 Hz), 2.27 (dq, *J* = 7.6, 14.8 Hz, 2H), 2.01 (dq, *J* = 7.2, 14.8 Hz, 2H), 1.09 (t, *J* = 7.2 Hz).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.2, 139.9, 132.4 (q, *J* = 34 Hz), 130.8 (d, *J* = 3 Hz), 130.4, 127.4 (quintet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.9, 77.8, 66.9, 23.5, 8.7.

**<sup>19</sup>F NMR** (376.5 MHz): δ -63.8.

**HRMS**: *m/z* calcd for C<sub>17</sub>H<sub>18</sub>F<sub>6</sub>NaO<sub>4</sub>S: 455.0728; Found: 455.0726.

**Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-propylpentanoate (3.81)**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 5.83 (ddt, *J* = 16.4, 10.4, 6.0 Hz, 1H), 5.27 – 5.33 (m, 2H), 4.56 (d, *J* = 6.0 Hz, 2H), 2.11 (m, 2H), 1.90 (m, 2H), 1.67 – 1.56 (m, 2H), 1.40 – 1.29 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 6H).

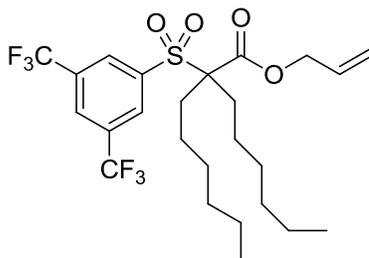
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.4, 139.7, 132.3 (q, *J* = 35 Hz), 130.8 (d, *J* = 3 Hz), 130.5, 127.4 (quintet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.8, 66.8, 32.7, 17.5, 14.3.

**<sup>19</sup>F NMR** (376.5 MHz): δ - 63.8.

**IR** (film): 3089, 2970, 2939, 2879, 1745, 1731, 1651, 1626, 1605, 1467, 1359, 1334, 1315, 1281, 1187, 1149, 1098.

**HRMS**: *m/z* calcd for C<sub>19</sub>H<sub>22</sub>F<sub>6</sub>NaO<sub>4</sub>S: 483.1041; Found: 483.1032.

**Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-hexyloctanoate (3.82)**



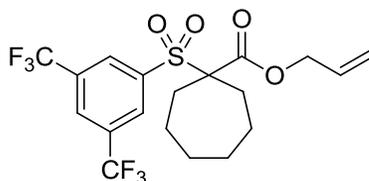
**Yield:** 48%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.27 (s, 2H), 8.14 (s, 1H), 5.83 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.27 – 5.33 (m, 2H), 4.56 (d, *J* = 6.0 Hz, 2H), 2.08 – 2.15 (m, 2H), 1.89 – 1.95 (m, 2H), 1.20 – 1.37 (m, 16H), 0.86 – 0.88 (m, 6H).

**<sup>19</sup>F NMR** (376.5 MHz): δ – 63.8.

**HRMS:** *m/z* calcd for C<sub>25</sub>H<sub>34</sub>F<sub>6</sub>NaO<sub>4</sub>S: 567.1980; Found: 567.1992.

**Allyl 1-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)cycloheptanecarboxylate (3.83)**



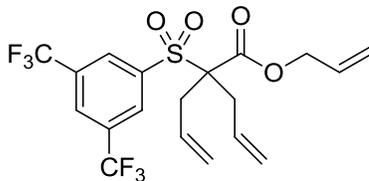
**Yield:** 27%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.25 (s, 2H), 8.14 (s, 1H), 5.85 (ddt, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.32 (d, *J* = 17.6 Hz + additional unresolved fine coupling, 1H), 5.29 (d, *J* = 10.0 Hz, + additional unresolved fine coupling, 1H), 4.61 (d, *J* = 6.0 Hz, 2H), 2.25 – 2.40 (m, 4H), 1.81 – 1.87 (m, 2H), 1.43 – 1.64 (m, 6H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.9, 139.1, 132.4 (q, *J* = 35 Hz), 130.8 (unresolved fine coupling), 130.5, 127.5 (app t, *J* = 4 Hz), 122.4 (q, *J* = 272 Hz), 119.9, 77.6, 67.1, 30.9, 29.2, 23.4.

**<sup>19</sup>F NMR** (376.5 MHz):  $\delta$  – 63.8.

**Allyl 2-allyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)pent-4-enoate (3.84)**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.30 (s, 2H), 8.16 (s, 1H), 5.89 – 5.78 (m, 3H), 5.35 – 5.18 (m, 6H), 4.59 (d,  $J$  = 6.0 Hz, 2H), 2.93 (dd AB,  $J$  = 14.4, 6.8 Hz, 2H), 2.80 (dd AB,  $J$  = 14.4, 6.8 Hz, 2H).

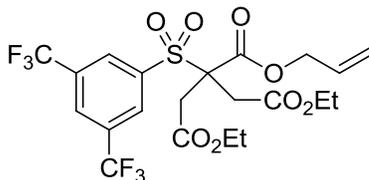
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 166.5, 139.4, 132.5 (q,  $J$  = 34 Hz), 130.9 (d,  $J$  = 3 Hz), 130.3, 127.7 (quintet,  $J$  = 3 Hz), 122.4 (q,  $J$  = 271 Hz), 120.9, 76.0, 67.2, 35.0.

**<sup>19</sup>F NMR** (376.5 MHz):  $\delta$  – 63.8.

**IR** (film): 3087, 3026, 2987, 2954, 1859, 1733, 1641, 1626, 1605, 1439, 1359, 1339, 1316, 1281, 1214, 1188, 1147, 1100.

**HRMS**:  $m/z$  calcd for C<sub>19</sub>H<sub>18</sub>F<sub>6</sub>NaO<sub>4</sub>S: 479.0728; Found: 479.0730.

**2-allyl 1,3-diethyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)propane-1,2,3-tricarboxylate (3.85)**



**Yield**: 53%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.33 (s, 2H), 8.20 (s, 1H), 5.83 (ddt,  $J$  = 17.2, 10.8, 6.0 Hz, 1H), 5.31 (overlapping doublets, 2H), 4.61 (d,  $J$  = 6.0 Hz, 2H), 4.22 –

4.17 (m, 4H), 3.44 (d AB,  $J = 16.8$  Hz, 2H), 3.36 (d AB,  $J = 16.8$  Hz, 2H), 1.31 (t,  $J = 7.2$  Hz, 6H).

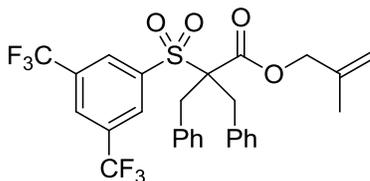
$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz): 168.9, 165.7, 137.3, 132.8 (q,  $J = 35$  Hz), 131.1 (unresolved coupling), 130.2, 128.3, 122.3 (q,  $J = 272$  Hz), 120.0, 72.6, 67.7, 61.5, 33.3, 13.9.

$^{19}\text{F NMR}$  (376.5 MHz):  $\delta - 63.9$ .

**IR** (film): 3088, 2987, 2945, 2910, 1741, 1650, 1626, 1606, 1449, 1416, 1397, 1359, 1344, 1282, 1186, 1149, 1106, 1062, 1029.

**HRMS**:  $m/z$  calcd for  $\text{C}_{21}\text{H}_{22}\text{F}_6\text{NaO}_3\text{S}$ : 571.0837; Found: 571.0845.

**2-Methylallyl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.86)**



**Yield**: 90%.

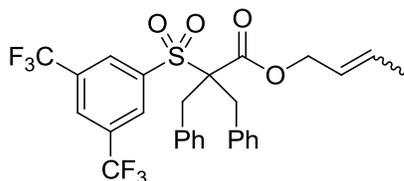
$^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.14 (s, 2H), 8.01 (s, 1H), 4.97 (s, 2H), 4.54 (s, 2H), 3.54 (d,  $J = 14.0$  Hz, 2H), 3.46 (d,  $J = 14.0$  Hz, 2H), 1.62 (s, 3H).

$^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz): 167.2, 141.4, 138.0, 133.7, 132.2 (q,  $J = 35$  Hz), 130.9, 128.3, 127.7, 127.2 (app t,  $J = 3$  Hz), 122.4 (q,  $J = 272$  Hz), 115.3, 79.4, 69.9, 39.5, 19.5.

$^{19}\text{F NMR}$  (376.5 MHz):  $\delta - 63.6$ .

**HRMS**:  $m/z$  calcd for  $\text{C}_{28}\text{H}_{24}\text{F}_6\text{NaO}_4\text{S}$ : 593.1197; Found: 593.1184.

**But-2-en-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.87)**



**Yield:** 94%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.16 (s, 2H), 8.02 (s, 1H), 7.21 (br s, 10H), 5.77 – 5.85 (m, 1H – mixture of cis/trans), 5.44 – 5.52 (m, 1H – mixture of cis/trans), 4.70 (d, *J* = 6.8 Hz, 2H, minor cis isomer – 5 %), 4.56 (d, *J* = 6.8 Hz, 2H, major trans isomer – 95%), 3.51 (d, *J* = 14.0 Hz, 2H), 3.42 (d, *J* = 14.0 Hz, 2H), 1.72 (d, *J* = 6.4 Hz, 3H, major trans isomer), 1.68 (d, *J* = 7.6 Hz, 3H, minor cis isomer) .

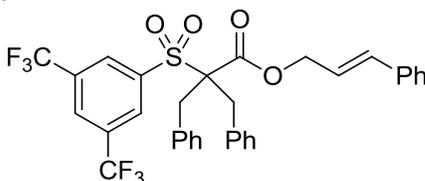
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.1, 141.5, 133.8, 133.7, 132.0 (q, *J* = 34 Hz), 130.9 (broadened shoulder; overlapping peak likely), 128.2, 127.6, 127.1 (app t, *J* = 4 Hz), 122.3 (q, *J* = 272 Hz), 123.1, 79.2, 67.3 (major isomer), 61.9 (minor isomer), 39.5, 17.6 (major isomer), 13.0 (minor isomer).

**<sup>19</sup>F NMR** (376.5 MHz): δ -63.6.

**IR** (film): 3091, 3066, 3034, 2943, 1733, 1497, 1456, 1357, 1335, 1315, 1280, 1186, 1145, 1098.

**HRMS:** *m/z* calcd for C<sub>28</sub>H<sub>24</sub>F<sub>6</sub>NaO<sub>4</sub>S: 593.1197; Found: 593.1195.

**Cinnamyl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.88)**



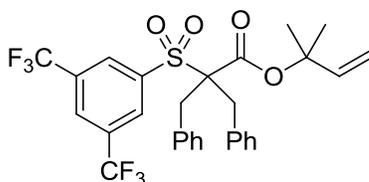
**Yield:** 75%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.18 (s, 2H), 8.00 (s, 1H), 7.34 – 7.35 (m, 5H), 7.19 – 7.22 (m, 10H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.13 (dt, *J* = 16.0, 6.8 Hz, 1H), 4.78 (d, *J* = 6.4 Hz, 2H), 3.53 (d, *J* = 14.0 Hz, 2H), 3.45 (d, *J* = 14.0 Hz, 2H).

**<sup>19</sup>F NMR** (376.5 MHz): δ – 63.6.

**HRMS**: *m/z* calcd for C<sub>33</sub>H<sub>26</sub>F<sub>6</sub>NaO<sub>4</sub>S: 655.1354; Found: 655.1363.

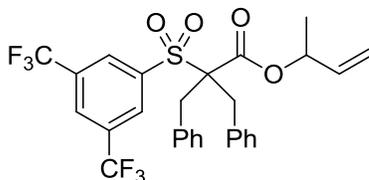
**2-Methylbut-3-en-2-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate**



**Yield**: 44% (starting from impure material).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.17 (s, 2H), 8.02 (s, 1H), 7.19 – 7.21 (m, 10H), 5.21 – 5.26 (m, 1H), 4.64 (d, *J* = 7.6 Hz, 2H), 3.50 (d, *J* = 14 Hz, 2H), 3.41 (d, *J* = 14 Hz, 2H), 1.76 (s, 3H), 1.67 (s, 3H).

**But-3-en-2-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.89)**



**Yield**: 89%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.19 (s, 2H), 8.03 (s, 1H), 5.71 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.39 (dq, *J* = 6.4, 6.4 Hz, 1H), 5.23 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 3.42 – 3.55 (m, 4H), 1.27 (d, *J* = 6.4 Hz, 3H).

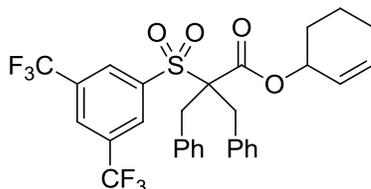
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 166.9, 141.3, 135.7, 133.74, 133.69, 132.0 (q, *J* = 5 Hz), 131.0 (d, *J* = 3 Hz), 130.9, 128.1, 127.59, 127.55, 127.1 (app t, *J* = 3 Hz), 122.4 (q, *J* = 271 Hz), 117.9, 79.1, 74.7, 39.5, 39.3, 19.3.

**<sup>19</sup>F NMR** (376 MHz): δ - 63.6.

**IR** (film): 3091, 3067, 3035, 2987, 2936, 1726, 1625, 1603, 1497, 1456, 1358, 1336, 1315, 1280, 1187, 1145, 1099, 1034.

**HRMS**: *m/z* calcd for C<sub>28</sub>H<sub>24</sub>F<sub>6</sub>NaO<sub>4</sub>S: 593.1197; Found: 593.1201.

**Cyclohex-2-en-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.90)**



**Yield**: 74%.

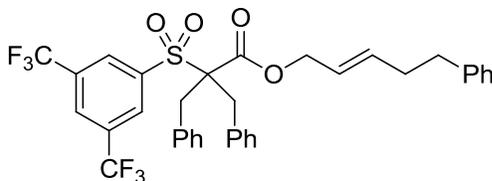
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.19 (s, 2H), 8.01 (s, 1H), 7.20 – 7.26 (m, 10H), 5.99 (dm, *J* = 9.6 Hz, unresolved, 1H), 5.60 (dm, *J* = 7.2 Hz, unresolved, 1H), 5.27 (br s, 1H), 3.49 (m, 4H), 1.96 – 2.09 (m, 2H), 1.77 – 1.83 (m, 1H), 1.54 – 1.58 (m, 6H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 167.3, 141.6, 134.4, 133.8 (d, *J* = 5 Hz), 132.0 (q, *J* = 34 Hz), 131.0, 130.9, 128.2, 127.6, 127.1 (m, unresolved), 123.8, 122.4 (q, *J* = 272 Hz), 79.1, 71.8, 39.6, 27.6, 24.7, 18.5.

**<sup>19</sup>F NMR** (376 MHz): δ - 63.6.

**HRMS**: *m/z* calcd for C<sub>30</sub>H<sub>26</sub>F<sub>6</sub>NaO<sub>4</sub>S: 619.1354; Found: 619.1367.

**(E)-5-phenylpent-2-en-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.91)**



**Yield:** 86%.

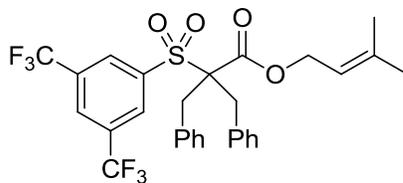
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.17 (s, 2H), 8.02 (s, 1H), 8.00 (s, minor isomer), 7.06 – 7.35 (m, 15H), 5.82 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.48 (dt, *J* = 15.2, 6.8 Hz, 1H), 4.56 (d, *J* = 6.4 Hz, 2H), 3.50 (d, *J* = 14 Hz, 2H), 3.41 (d, *J* = 14 Hz, 2H), 2.78 (m, minor isomer), 2.68 (t, *J* = 7.2 Hz, 2H), 2.54 (m, minor isomer), 2.37 (dt, *J* = 7.2, 7.2 Hz, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.4 (minor isomer), 167.2, 141.5, 141.2, 137.7, 133.8, 133.6 (minor isomer), 132.2 (q, *J* = 34 Hz), 131.1, 131.0, 130.9, 129.0 (minor isomer), 128.7 (minor isomer), 128.4 (d, *J* = 5 Hz), 128.2, 127.8, 127.2 (unresolved fine coupling), 126.0, 122.6, 122.4 (q, *J* = 272 Hz), 79.3, 68.4 (minor isomer), 67.2, 39.7, 33.1, 34.0.

**<sup>19</sup>F NMR** (376 MHz): δ – 63.58, -63.62 (minor isomer, 19% based on relative integration).

**HRMS:** *m/z* calcd for C<sub>35</sub>H<sub>30</sub>F<sub>6</sub>NaO<sub>4</sub>S: 683.1667; Found: 683.1683.

**3-methylbut-2-en-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.92)**



**Yield:** 84%.

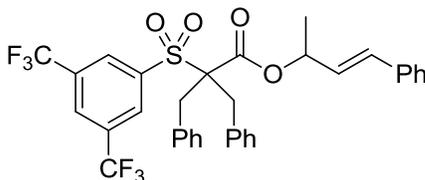
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.18 (s, 2H), 8.02 (s, 1H), 5.24 (tm, *J* = 7.6 Hz, unresolved, 1H), 4.64 (d, *J* = 7.6 Hz, 2H), 3.50 (d, *J* = 14.0 Hz, 2H), 3.41 (d, *J* = 14.0 Hz, 2H), 1.76 (s, 3H), 1.67 (s, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.4, 141.5, 133.8, 132.0 (q, *J* = 34 Hz), 131.1 (d, *J* = 3 Hz), 131.0, 128.2, 127.7, 127.1 (septet, *J* = 3 Hz), 122.1 (q, *J* = 272 Hz), 116.7, 79.2, 63.4, 39.6, 25.7, 18.0.

**<sup>19</sup>F NMR** (376 MHz): δ -63.6.

**HRMS:** *m/z* calcd for C<sub>29</sub>H<sub>26</sub>F<sub>6</sub>NaO<sub>4</sub>S: 607.1354; Found: 607.1347.

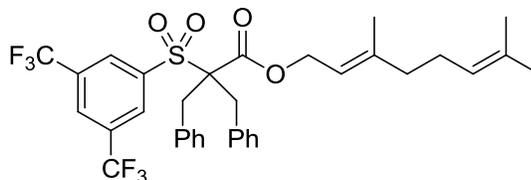
**(E)-4-phenylbut-3-en-2-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate**



**Yield:** 66% (contained impurities other than the minor cis isomer – NMR data shown for major product).

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.20 (s, 2H), 7.99 (s, 1H), 7.28 – 7.35 (m, 5H), 7.10 – 7.23 (m, 10H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.00 (dd, *J* = 16.0, 7.3 Hz, 1H), 5.58 (dq, *J* = 6.5, 6.5 Hz), 3.41 – 3.54 (m, 4H), 1.37 (d, *J* = 6.4 Hz, 3H).

**(*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl) sulfonyl)-3-phenylpropanoate (3.93)**



**Yield:** 90%.

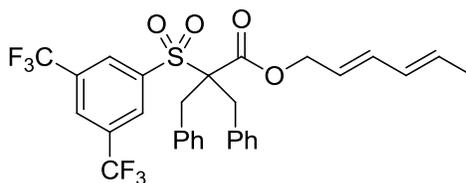
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.18 (s, 2H), 8.02 (s, 1H), 7.21 (br s, 10H), 5.23 (t, *J* = 7.2 Hz, 1H), 5.05 (br s w/ shoulder, 1H), 4.66 (d, *J* = 7.2 Hz, 2H), 3.49 (d, *J* = 14.0 Hz, 2H), 3.41 (d, *J* = 14.0 Hz, 2H), 2.05 – 2.07 (m, 4H), 1.67 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.4, 144.8, 141.5, 133.8, 132.0 (q, *J* = 35 Hz), 131.1 (unresolved fine coupling), 130.0, 128.2, 127.7, 127.1 (unresolved fine coupling), 123.4, 122.4 (q, *J* = 272 Hz), 116.3, 79.3, 63.4, 39.6, 39.5, 26.2, 25.6, 17.7, 16.4.

**<sup>19</sup>F NMR** (376 MHz): δ – 63.6.

**HRMS:** *m/z* calcd for C<sub>34</sub>H<sub>34</sub>F<sub>6</sub>NaO<sub>4</sub>S: 675.1980; Found: 675.1989.

**(2*E*,4*E*)-hexa-2,4-dien-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.94)**



**Yield:** 87%.

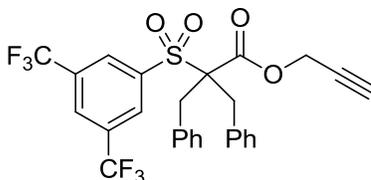
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.16 (s, 2H), 8.02 (s, 1H), 7.21 (br s, 10H), 6.22 (dd, *J* = 10.4, 15.2 Hz, 1H), 6.02 (m, 1H), 5.78 (ddt, *J* = 14.8, 6.8, 6.8 Hz, 1H), 5.48 (dt, *J* = 15.2, 6.8 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 2H), 3.51 (d, *J* = 14.0 Hz, 2H), 3.42 (d, *J* = 14.0 Hz, 2H), 1.78 (d, *J* = 6.8 Hz, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): 167.2, 141.5, 137.2, 130.7, 132.8, 132.1 (q, *J* = 34 Hz), 131.0, 130.0, 128.2, 127.7, 127.2 (unresolved septet), 122.4 (q, *J* = 271 Hz), 121.1, 79.3, 67.2, 39.6, 18.2.

**<sup>19</sup>F NMR** (376 MHz): δ – 63.6.

**HRMS:** *m/z* calcd for C<sub>30</sub>H<sub>26</sub>F<sub>6</sub>NaO<sub>4</sub>S: 619.1354; Found: 619.1337.

**Prop-2-yn-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.95)**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.20 (s, 2H), 8.04 (s, 1H), 7.23 (br s, 10H), 4.72 (d, *J* = 2.4 Hz, 2H), 3.53 (d, *J* = 14.0 Hz, 2H), 3.45 (d, *J* = 14.0 Hz, 2H), 2.53 (t, *J* = 2.4 Hz, 1H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 166.7, 141.2, 133.4, 132.2 (q, *J* = 34 Hz), 131.0 (unresolved fine splitting), 130.9, 128.3, 127.8, 127.3 (app t, *J* = 3 Hz), 122.3 (q, *J* = 272 Hz), 79.2, 75.5, 53.5, 39.5.

**<sup>19</sup>F NMR** (376 MHz): δ – 36.6.

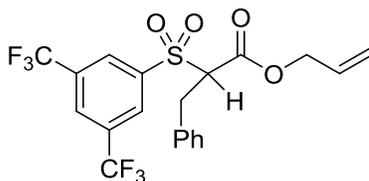
**IR** (film): 3288, 3090, 3067, 3035, 2936, 2134, 1743, 1625, 1603, 1497, 1456, 1357, 1335, 1315, 1280, 1184, 1145, 1097.

**HRMS**: m/z calcd for C<sub>27</sub>H<sub>20</sub>F<sub>6</sub>NaO<sub>4</sub>S: 577.0884; Found: 577.0895.

### General Procedure for Monoalkylation of Sulfones

A dry round-bottom flask was charged with the appropriate sulfone (1 equiv). Under an inert atmosphere, dry DMF (0.1 M relative to sulfone) was added via syringe. Sodium hydride (dry) was added (1.1 equiv) to this solution in 2-3 portions. The reaction mixture was allowed to stir for 30 minutes at room temperature. Typically, the reaction mixture turned yellow in color during this time. All alkyl halides were purified immediately prior to use by passage through a short column of activated basic alumina in a Pasteur pipet fitted with a cotton plug. Purified alkyl halide (1.2 equiv, for mono-benzyl; 1.3 equiv, for mono-ethyl) was added via syringe to flask. The reaction mixture stirred at room temperature until deemed complete by TLC. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl<sub>(aq)</sub>, then diluted with water (5x volume of DMF), then extracted five times with EtOAc. The combined organic extracts were washed once with water, once with brine, then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The material was purified by flash chromatography (typically 5% EtOAc/hexane) to give product.

### Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.96)



**Yield:** 40%.

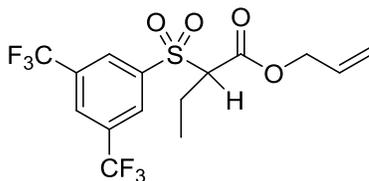
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.33 (s, 2H), 8.18 (s, 1H), 7.22 – 7.29 (m, 3H), 7.13 – 7.15 (m, 2H), 5.61 (ddt, *J* = 17.2, 10.8, 6.0 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 5.11 (dd, *J* = 17.2, 1.2 Hz, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.31 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.50 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.18 (dd, *J* = 11.6, 13.2 Hz, 1H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 164.5, 139.8, 134.5, 133.0 (q, *J* = 34 Hz), 130.9, 129.9 (d, *J* = 4 Hz), 129.0, 128.9, 128.0 (app t, *J* = 3 Hz), 127.7, 122.3 (q, *J* = 272 Hz), 119.8, 72.2, 67.0, 32.6.

**<sup>19</sup>F NMR** (376 MHz): δ – 63.8.

**HRMS:** *m/z* calcd for C<sub>20</sub>H<sub>16</sub>F<sub>6</sub>NaO<sub>4</sub>S: 489.0571; Found: 489.0570.

**Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)butanoate (3.97)**



**Yield:** 60%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.32 (s, 2H), 8.17 (s, 1H), 5.80 (ddt, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 2H), 3.98 (dd, *J* = 11.2, 3.6 Hz, 1H), 2.13 – 2.23 (m, 1H), 1.86 – 1.98 (m, 1H), 1.04 (t, *J* = 7.2 Hz).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 165.0, 139.8, 132.9 (q, *J* = 35 Hz), 130.4, 130.0 (unresolved fine coupling), 127.8 (unresolved fine coupling), 122.3 (q, *J* = 272 Hz), 120.2, 72.3, 67.1, 20.7, 11.4.

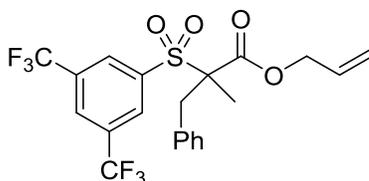
**<sup>19</sup>F NMR** (376 MHz): δ – 63.9.

**HRMS:** m/z calcd for C<sub>15</sub>H<sub>14</sub>F<sub>6</sub>NaO<sub>4</sub>S: 427.0415; Found: 427.0405.

### General Procedure for Differentially Substituted $\alpha,\alpha$ -Dialkylated Sulfones

A dry round-bottom flask was charged with the appropriate monoalkylated sulfone **3.98** or **3.99** (1 equiv). Under an inert atmosphere, dry DMF (0.1 M relative to sulfone) was added via syringe. Finely powdered anhydrous K<sub>2</sub>CO<sub>3</sub> (5 equiv) was added to the reaction mixture in a single portion. The reaction mixture was allowed to stir for 15 minutes at room temperature. Typically, the reaction mixture turned yellow in color during this time. All alkyl halides were purified immediately prior to use by passage through a short column of activated basic alumina in a Pasteur pipet fitted with a cotton plug. Purified alkyl halide (5 equiv, if volatile, including MeI, EtI, PrI, allyl iodide; 2.3 equiv, if not, including benzyl bromide, hexyl bromide) was added via syringe to flask. The reaction mixture stirred at room temperature until deemed complete by TLC. The reaction mixture was diluted with water (5x volume of DMF), then extracted five times with EtOAc. The combined organic extracts were washed once with water, once with brine, then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The material was purified by flash chromatography (typically 5% EtOAc/hexane) to give product.

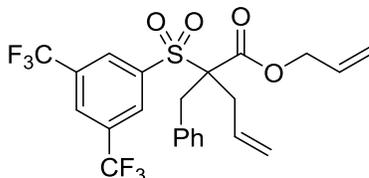
### Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-methyl-3-phenylpropanoate (**3.98**)



**Yield:** 69%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.34 (s, 2H), 8.19 (s, 1H), 7.21 – 7.27 (m, 3H), 7.05 – 7.08 (m, 2H), 5.80 (ddt, *J* = 17.6, 10.0, 6.0 Hz, 1H), 5.26 – 5.30 (m, 2H), 4.57 – 4.59 (m, 2H), 3.46 (d, *J* = 12.8 Hz, 1H), 3.12 (d, *J* = 12.8 Hz, 1H), 1.58 (s, 3H).

**Allyl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)pent-4-enoate (3.99)**



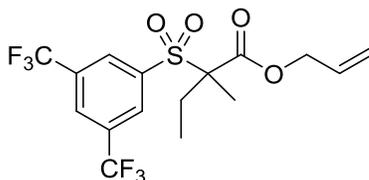
**Yield:** 79%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.35 (s, 2H), 8.15 (s, 1H), 5.93 – 6.03 (m, 1H), 5.82 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1H), 5.27 – 5.33 (m, 2H), 5.14 – 5.20 (m, 2H), 3.39 (d, *J* = 13.2 Hz, 2H), 3.34 (d, *J* = 13.2 Hz, 2H), 2.88 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.77 (dd, *J* = 15.6, 7.6 Hz, 1H).

**<sup>19</sup>F NMR** (376 MHz): δ – 63.8.

**HRMS:** *m/z* calcd for C<sub>23</sub>H<sub>20</sub>F<sub>6</sub>NaO<sub>4</sub>S: 529.0884; Found: 529.0859.

**Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-methylbutanoate (3.100)**



**Yield:** 94%.

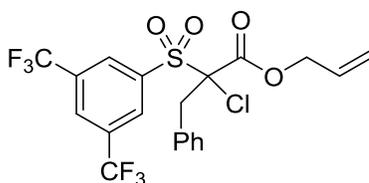
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 5.85 (ddt, *J* = 17.2, 11.6, 5.6 Hz, 1H), 5.35 – 5.28 (m, 2H), 4.56 – 4.66 (m, 2H), 2.10 (dq, *J* = 13.2, 7.6 Hz, 1H), 1.94 (dq, *J* = 13.2, 7.2 Hz, 1H), 1.67 (s, 3H), 0.94 (t, *J* = 7.2 Hz).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 167.3, 138.8, 132.5 (q, *J* = 35 Hz), 130.9 (unresolved), 130.5, 127.6 (septet, *J* = 4 Hz), 122.4 (q, *J* = 271 Hz), 120.0, 74.4, 67.1, 26.7, 15.2, 8.6.

**<sup>19</sup>F NMR** (376 MHz): δ – 63.8.

**HRMS:** *m/z* calcd for C<sub>16</sub>H<sub>16</sub>F<sub>6</sub>NaO<sub>4</sub>S: 441.0571; Found: 441.0570.

**Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-chloro-3-phenylpropanoate (3.101)**



The monobenzylated sulfone **3.98** (138 mg, 0.30 mmol, 1 equiv) was dissolved in THF (3 mL, 0.1 M relative to sulfone). Finely powdered K<sub>2</sub>CO<sub>3</sub> (207 mg, 1.50 mmol, 5 equiv) was added, and the flask contents were stirred for 15 min at room temperature. N-chlorosuccinimide (40 mg, 0.30 mmol, 1 equiv) was then added in a single portion. The reaction mixture was stirred overnight, then the solvent was removed in vacuo. The crude product was purified via flash chromatography (5% EtOAc/hexane) to give 116 mg (78%) chlorinated product.

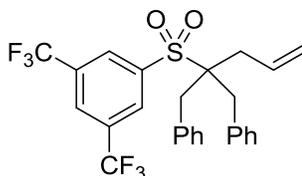
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.39 (s, 2H), 8.20 (s, 1H), 5.77 (ddt, *J* = 17.6, 10.8, 6.0 Hz, 1H), 5.26 (overlapping dd, 2H), 4.63 (dd, *J* = 12.8, 6.0 Hz, 1H), 4.55 (dd, *J* = 12.8, 6.0 Hz, 1H), 4.13 (d, *J* = 13.6 Hz, 1H), 3.52 (d, *J* = 13.6 Hz, 1H).

**<sup>19</sup>F NMR** (376 MHz): δ -63.8.

### General Procedure for Pd-Catalyzed Decarboxylative Allylation

A flame-dried Schlenk flask was charged with  $\eta^5$ -cyclopentadienyl- $\eta^3$ -1-phenylallylpalladium and Xantphos, then the flask was purged and backfilled three times with argon. Freshly distilled THF was added via syringe. The flask was immersed in a pre-heated 50 °C oil bath for 60 minutes to form the active catalyst. The substrate was dissolved in 1 mL of dry THF and added dropwise to the catalyst solution via syringe. The reaction was monitored by TLC until starting material is completely consumed. The reaction was then quenched with 10 mL brine, and extracted three times with 15 mL EtOAc. The combined organic extracts were washed once with 50 mL brine, then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (2.5% - 10% EtOAc/hexanes).

### (2-allyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)propane-1,3-diyl)dibenzene (3.102)



**Yield:** 79%.

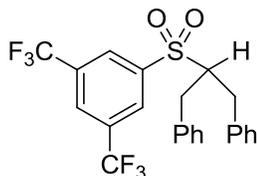
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.04 (s, 2H), 7.95 (s, 1H), 7.20 – 7.24 (m, 10H), 6.06 (ddt,  $J$  = 16.8, 10.4, 6.4 Hz, 1H), 5.29 (dd,  $J$  = 10.4, 1.6 Hz, 1H), 5.23 (dd,  $J$  = 16.8 Hz, 1.6 Hz, 1H), 3.34 (d,  $J$  = 14.0 Hz, 2H), 3.15 (d,  $J$  = 14.0 Hz, 2H), 2.63 (d,  $J$  = 6.8 Hz, some unresolved fine coupling, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 141.1, 134.3, 131.9 (q, *J* = 34 Hz), 131.7, 131.3, 130.8 (d, *J* = 3 Hz), 128.4, 127.7, 126.9 (unresolved mult), 122.3 (q, *J* = 271 Hz), 120.6, 72.3, 39.1, 37.2.

**<sup>19</sup>F NMR** (376 MHz): δ – 63.6.

**(2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)propane-1,3-diyl)dibenzene**

**(3.119)**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.04 (s, 2H), 7.85 (s, 1H), 7.08 – 7.15 (m, 6H), 6.40 – 6.96 (m, 4H), 3.80 (quintet, *J* = 6.8 Hz, 1H), 3.36 (dd, *J* = 14.4, 6.4 Hz, 2H), 2.98 (dd, *J* = 14.8, 6.8 Hz, 2H).

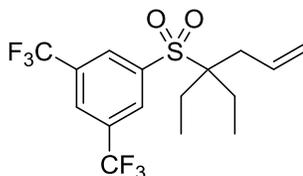
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 142.2, 136.3, 132.6 (q, *J* = 34 Hz), 128.83, 128.75, 128.6 (unresolved fine coupling), 127.1, 126.9 (quintet, *J* = 4 Hz), 122.2 (q, *J* = 272 Hz), 67.5, 33.7.

**<sup>19</sup>F NMR** (376 MHz): δ - 63.9.

**IR** (film): 3066, 3031, 2932, 1626, 1603, 1498, 1456, 1359, 1328, 1311, 1280, 1184, 1144, 1104, 1030.

**HRMS**: *m/z* calcd for C<sub>23</sub>H<sub>18</sub>F<sub>6</sub>NaO<sub>2</sub>S: 495.0829; Found: 495.0827.

**1-((3-ethylhex-5-en-3-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.126)**



**Yield**: 76%.

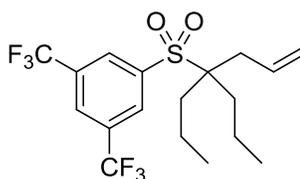
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.32 (s, 2H), 8.14 (s, 1H), 5.82 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.10 – 5.16 (overlapping dd, 2H), 2.46 (d, *J* = 6.8 Hz, 2H), 1.85 (dq, *J* = 15.2, 7.6 Hz, 2H), 1.76 (dq, *J* = 15.2, 7.2 Hz, 2H), 1.07 (t, *J* = 7.6 Hz, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 140.3, 132.6 (q, *J* = 34 Hz), 131.3, 130.5 (d, *J* = 3 Hz), 127.1 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.5, 70.0, 37.0, 25.1, 8.21.

**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**HRMS**: *m/z* calcd for C<sub>16</sub>H<sub>18</sub>F<sub>6</sub>NaO<sub>2</sub>S: 411.0829; Found: 411.0817.

**1-((4-propylhept-1-en-4-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.127)**



**Yield**: 82%.

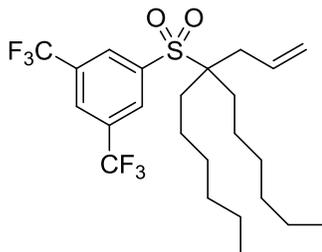
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.31 (s, 2H), 8.15 (s, 1H), 5.81 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.09 – 5.16 (overlapping dd, 2H), 2.46 (d, *J* = 6.8 Hz, 2H), 1.63 – 1.70 (m, 4H), 1.45 – 1.58 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 140.1, 132.6 (q, *J* = 34 Hz), 131.5, 130.5 (d, *J* = 3 Hz), 127.1 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.5, 70.1, 37.7, 34.9, 16.9, 14.5.

**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**HRMS**: *m/z* calcd for C<sub>18</sub>H<sub>22</sub>F<sub>6</sub>NaO<sub>2</sub>S: 439.1142; Found: 439.1135.

**1-((7-allyltridecan-7-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.128)**



**Yield:** 86%.

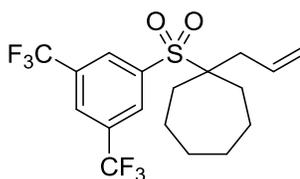
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.31 (s, 2H), 8.14 (s, 1H), 5.81 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.09 – 5.16 (overlapping doublets, 2H), 2.46 (d, *J* = 7.2 Hz, 2H), 1.65 – 1.69 (m, 4H), 1.46 – 1.47 (m, 4H), 1.20 – 1.35 (br s, w/ shoulder, 12H), 0.88 (t, *J* = 6.8 Hz, 6H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 140.1, 132.6 (q, *J* = 34 Hz), 131.5, 130.5 (unresolved fine coupling), 127.1 (unresolved fine coupling), 122.4 (q, *J* = 272 Hz), 119.5, 70.1, 37.6, 32.7, 31.5, 29.8, 23.4, 22.6, 13.9.

**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**HRMS:** *m/z* calcd for C<sub>24</sub>H<sub>34</sub>F<sub>6</sub>NaO<sub>2</sub>S: 523.2081; Found: 523.2080.

**1-allyl-1-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)cycloheptane (3.129)**



**Yield:** 65%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.33 (s, 2H), 8.15 (s, 1H), 5.93 (ddt, *J* = 17.2, 10.4, 7.6 Hz, 1H), 5.17 (d, *J* = 9.6 Hz, 1H), 5.10 (dd, *J* = 17.2, 1.2 Hz, 1H), 2.40 (d, *J* = 7.2 Hz, 2H), 2.25 (dd, *J* = 15.2, 10.0 Hz, 2H), 1.64 – 1.79 (m, 4H), 1.40 – 1.60 (m, 6H).

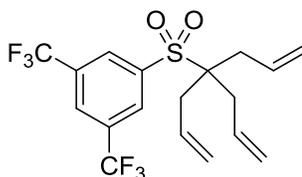
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 139.7, 132.6 (q, *J* = 35 Hz), 132.0, 130.8 (unresolved fine coupling), 127.1 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.5, 70.4, 41.3, 32.9, 30.9, 23.4.

**<sup>19</sup>F NMR** (376 MHz): δ -63.8.

**HRMS:** *m/z* calcd for C<sub>18</sub>H<sub>20</sub>F<sub>6</sub>NaO<sub>2</sub>S: 437.0986; Found: 437.0966.

**1-((4-allylhepta-1,6-dien-4-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene**

**(3.130)**



Yield: 85%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.35 (s, 2H), 8.15 (s, 1H), 5.89 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 3H), 5.17 (d, *J* = 10.8 Hz, 3H), 5.16 (d, *J* = 17.2 Hz, 3H), 2.53 (d, *J* = 6.8 Hz, 6H).

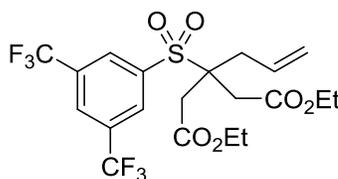
**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 139.7, 132.5 (q, *J* = 34 Hz), 131.1 (broadened; appears to be overlapping peaks), 127.5 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 120.2, 69.0, 37.3.

**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**HRMS:** *m/z* calcd for C<sub>18</sub>H<sub>18</sub>F<sub>6</sub>NaO<sub>2</sub>S: 435.0829; Found: 435.0823.

**Diethyl 3-allyl-3-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)pentanedioate**

**(3.131)**



Yield: 88%.

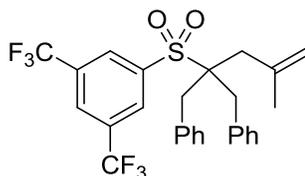
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.46 (s, 2H), 8.18 (s, 1H), 5.96 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 5.17 (d, *J* = 18.0 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 4H), 3.06 (d, *J* = 16.4 Hz, 2H), 2.99 (d, *J* = 16.8 Hz, 2H), 2.75 (d, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 6H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.9, 138.5, 132.8 (q, *J* = 34 Hz), 131.1 (d, *J* = 4 Hz), 130.7, 127.8 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 120.9, 67.3, 61.2, 37.8, 35.1, 13.9.

**<sup>19</sup>F NMR** (376 MHz): δ -63.8.

**HRMS**: *m/z* calcd for C<sub>20</sub>H<sub>22</sub>F<sub>6</sub>NaO<sub>6</sub>S: 527.0939; Found: 527.0919.

**(2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-(2-methylallyl)propane-1,3-diyl)dibenzene (3.132)**



**Yield**: 69%.

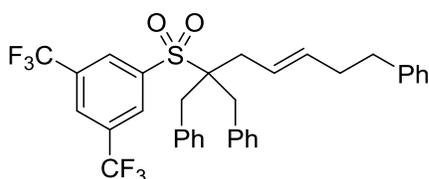
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.87 (s, 1H), 7.82 (s, 2H), 7.31 – 7.32 (m, 4H), 7.25 – 7.27 (m, 6H), 5.17 (s, 1H), 5.14 (s, 1H), 3.34 (s, 4H), 2.62 (s, 2H), 1.89 (s, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 141.8, 139.7, 134.7, 131.7 (q, *J* = 34 Hz), 131.5, 130.3, 128.4, 127.7, 126.6 (unresolved fine coupling), 122.3 (q, *J* = 272 Hz), 118.2, 73.6, 40.5, 39.2, 26.0.

**<sup>19</sup>F NMR** (376 MHz): δ – 65.5.

**HRMS**: *m/z* calcd for C<sub>27</sub>H<sub>24</sub>F<sub>6</sub>KO<sub>2</sub>S: 565.1038; Found: 565.1048.

**(E)-6-benzyl-6-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)hept-3-ene-1,7-diyl)dibenzene (3.137)**



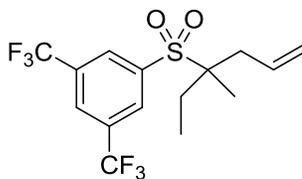
**Yield:** 37%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.96 (s, 2H), 7.92 (s, 1H), 7.16 – 7.30 (m, 15H), 5.60 – 5.65 (m, 2H), 3.32 (d, *J* = 14.0 Hz, minor isomer), 3.26 (d, *J* = 14.0 Hz, 2H, major isomer), 3.09 (d, *J* = 14.0 Hz, 2H, major isomer), 3.06 (d, *J* = 14.0 Hz, minor isomer), 2.71 (t, *J* = 7.2 Hz, 2H, major isomer), 2.67 (t, *J* = 7.6 Hz, minor isomer, partially obscured by triplet at 2.71), 2.50 – 2.60 (br s with shoulder, 2H), 2.35 – 2.45 (m, 2H), 2.20 – 2.30 (m, minor isomer).

**<sup>19</sup>F NMR** (376 MHz): δ -63.5 (major isomer), -63.6 (minor isomer).

**HRMS:** *m/z* calcd for C<sub>34</sub>H<sub>30</sub>F<sub>6</sub>NaO<sub>2</sub>S: 639.1768; Found: 639.1743.

**1-((3-methylhex-5-en-3-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.138)**



**Yield:** 57%.

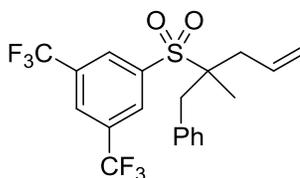
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.32 (s, 2H), 8.16 (s, 1H), 5.82 (ddt, *J* = 17.6, 10.0, 7.6 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 5.15 (dd, *J* = 17.2, 1.2 Hz, 1H), 2.60 (dd, *J* = 14.8, 7.2 Hz, 1H), 2.37 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.87 (dq, *J* = 14.4, 7.6 Hz, 1H), 1.71 (dq, *J* = 14.8, 7.6 Hz, 1H), 1.06 (t, *J* = 7.2 Hz, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 139.3, 132.7 (q, *J* = 35 Hz), 131.3, 130.6 (unresolved fine splitting), 127.2 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.9, 66.7, 37.5, 26.4, 19.5, 8.3.

**<sup>19</sup>F NMR** (376 MHz): δ -63.8.

**HRMS:** *m/z* calcd for C<sub>15</sub>H<sub>16</sub>F<sub>6</sub>NaO<sub>2</sub>S: 397.0673; Found: 397.0649.

**1-((2-methyl-1-phenylpent-4-en-2-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.139)**



**Yield:** 90%.

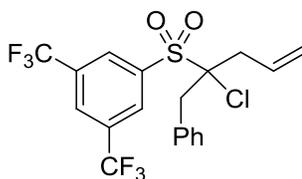
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.35 (s, 2H), 8.16 (s, 1H), 7.26 – 7.30 (m, 3H), 7.14 – 7.16 (m, 2H), 5.90 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.16 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.07 (dd, *J* = 16.8, 1.6 Hz, 1H), 3.16 (d, *J* = 13.6 Hz, 1H), 3.08 (d, *J* = 13.2 Hz, 1H), 2.46 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.36 (dd, *J* = 15.6, 6.8 Hz, 1H), 1.29 (s, 3H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 139.3, 134.0, 132.7 (q, *J* = 34 Hz), 131.7, 131.0, 130.9 (d, *J* = 3 Hz), 128.4, 127.5, 127.3 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.5, 67.4, 39.0, 38.3, 19.5.

**<sup>19</sup>F NMR** (376 MHz): δ -63.8.

**HRMS:** *m/z* calcd for C<sub>20</sub>H<sub>18</sub>F<sub>6</sub>NaO<sub>2</sub>S: 459.0829; Found: 459.0814.

**1-((2-chloro-1-phenylpent-4-en-2-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.140)**



**Yield:** 90%.

**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.41 (s, 2H), 8.16 (s, 1H), 7.31 (s, 5H), 5.83 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.16 – 5.23 (overlapping dd, 2H), 3.64 (d, *J* = 14.0 Hz, 1H), 3.39 (d, *J* = 14.4 Hz, 1H), 2.91 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.78 (dd, *J* = 15.6, 6.4 Hz, 1H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 137.9, 132.5 (q, *J* = 34 Hz), 132.2, 131.9, 131.8, 131.4, 130.2, 128.4, 128.1, 127.9 (septet, *J* = 3 Hz), 122.3 (q, *J* = 271 Hz), 120.7, 87.9, 40.9, 40.8 .

**<sup>19</sup>F NMR** (376 MHz): δ -63.8.

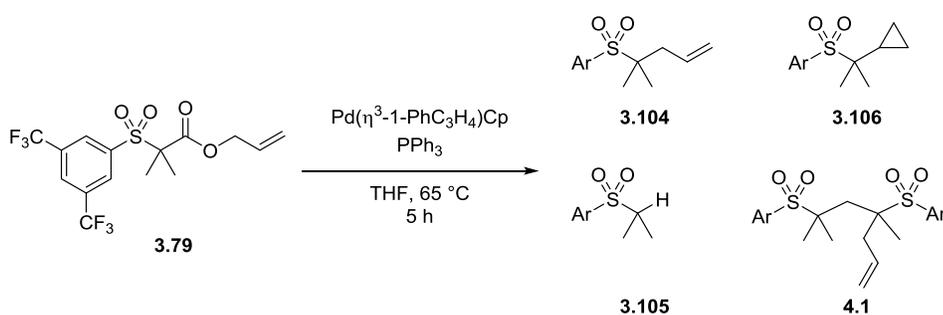
**HRMS:** *m/z* calcd for C<sub>19</sub>H<sub>15</sub>ClF<sub>6</sub>NaO<sub>2</sub>S: 479.0283; Found: 479.0285.

## Chapter 4 : Mechanistic Studies

### 4.1 Introduction

As discussed in previous sections, the appearance of a protonated byproduct in DcA reactions is quite common, however current mechanistic understanding doesn't account for its formation in the case of  $\alpha,\alpha$ -dialkylated substrates. A detailed isotope labelling study was undertaken to determine if the origin of the proton is from within the substrate itself. We also desired to gain some insight into the reasons for the dramatically different reactivity for the  $\alpha,\alpha$ -dimethyl substrate.

Conditions were determined that at least induced consumption of all starting material. It was required to heat the reaction mixture to 65 °C and maintain that temperature for approximately 5 hours. When this reaction was performed on a larger than usual scale, so that reasonable amounts of each product could be obtained for characterization, a fourth product **4.1** was obtained. This product was determined to be a unique dimeric product that appears to be the result of a C-H activation on the homoallylic sulfone product (Scheme 4.1).



## 4.2 Protonation

Along with the literature for DcA, there exists a smaller subset of literature that describes Pd-catalyzed decarboxylative protonation. It was recognized that the protonated product could be a useful pathway to  $\alpha$ -substituted ketones, and conditions were developed that were believed to promote protonation. The substrates for these reactions are the corresponding allyl esters.

### 4.2.1 Literature Review of Protonation Examples

Tsuji and co-workers reported the exceptionally mild Pd-catalyzed decarboxylative protonation protocol for  $\beta$ -keto allyl esters in 1985.<sup>107</sup> This

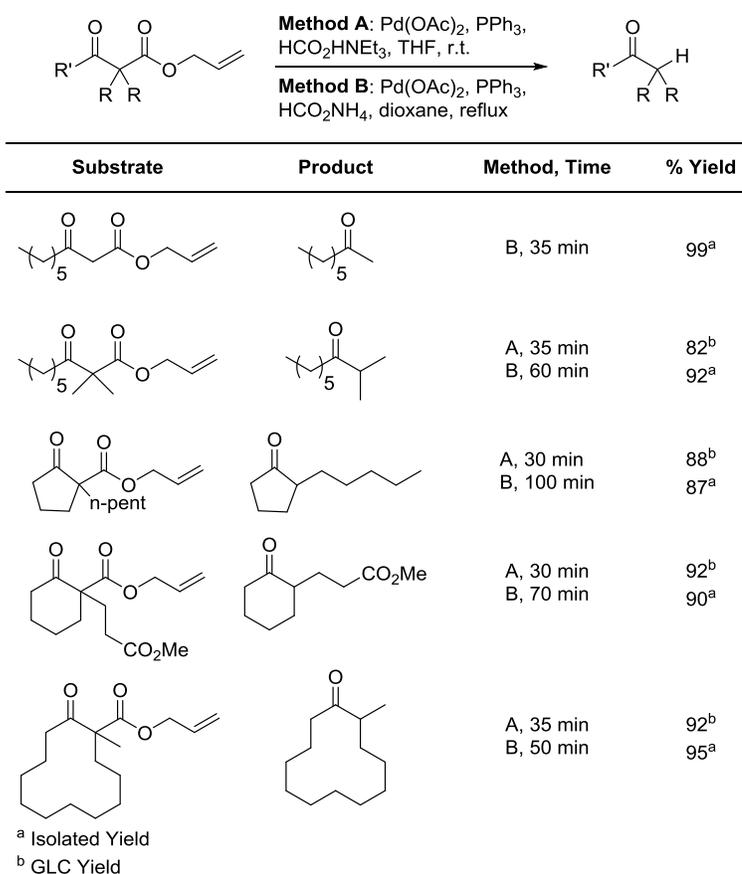


Figure 4.1. Tsuji's Pd-catalyzed decarboxylative protonation.

methodology was a mild and convenient route to  $\alpha$ -alkylated or  $\alpha,\alpha$ -dialkylated ketones that avoided issues associated with ketone enolate alkylation (strong bases, regiochemical issues, etc.). Selected examples are shown in Figure 4.1. The proposed mechanism (Figure 4.2) starts with the oxidative addition of the allyl ester to Pd(0), yielding the  $\pi$ -allyl Pd carboxylate species. An ammonium formate is proposed to react with the  $\pi$ -allyl Pd species, with concomitant decarboxylation and protonation to yield the ketone, along with a  $\pi$ -allyl Pd species with a bound formate.

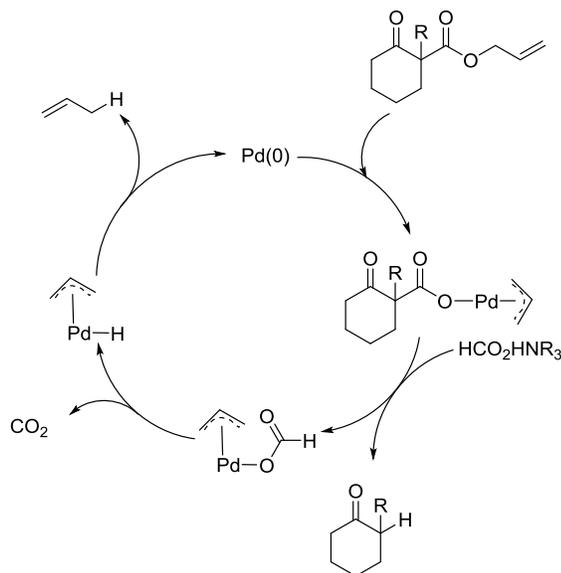
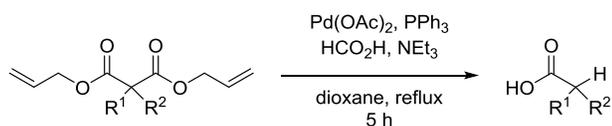


Figure 4.2. Tsuji's proposed catalytic cycle for Pd-catalyzed decarboxylative protonation.

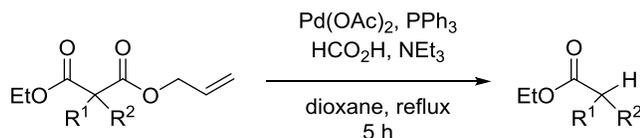
In a follow up paper in 1989, Tsuji reported on decarboxylative protonation of substituted malonate esters.<sup>108</sup> When diallyl malonates were employed, the monocarboxylic acid was obtained (Figure 4.3), while the use of mixed malonate esters (ethyl and allyl) resulted in ester products (Figure 4.4). These conditions are



R <sup>1</sup>	R <sup>2</sup>	yield, %
n-C <sub>6</sub> H <sub>13</sub>	-H	80
n-C <sub>6</sub> H <sub>13</sub>	-CH <sub>2</sub> Ph	83
TBDPSO-(CH <sub>2</sub> ) <sub>4</sub>	-H	67
AcO(CH <sub>2</sub> ) <sub>4</sub>	-CH <sub>2</sub> Ph	86

Figure 4.3. Tsuji's Pd-catalyzed decarboxylative protonation of diallyl malonate esters.

a mild alternative to saponification/heating or even Krapcho decarboxylation that would typically be performed on these substrates.



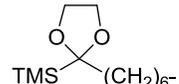
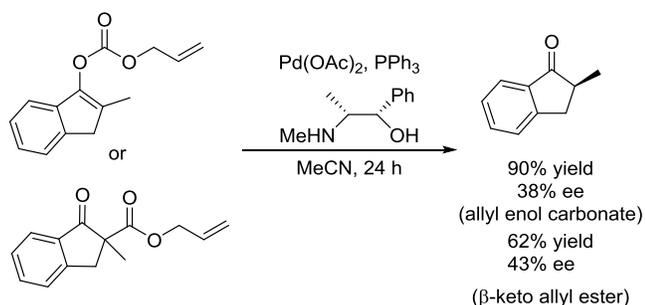
R <sup>1</sup>	R <sup>2</sup>	yield, %
THPO-(CH <sub>2</sub> ) <sub>4</sub>	-H	70
THPO-(CH <sub>2</sub> ) <sub>4</sub>	-CH <sub>2</sub> Ph	90
	EtO <sub>2</sub> CCH <sub>2</sub>	96

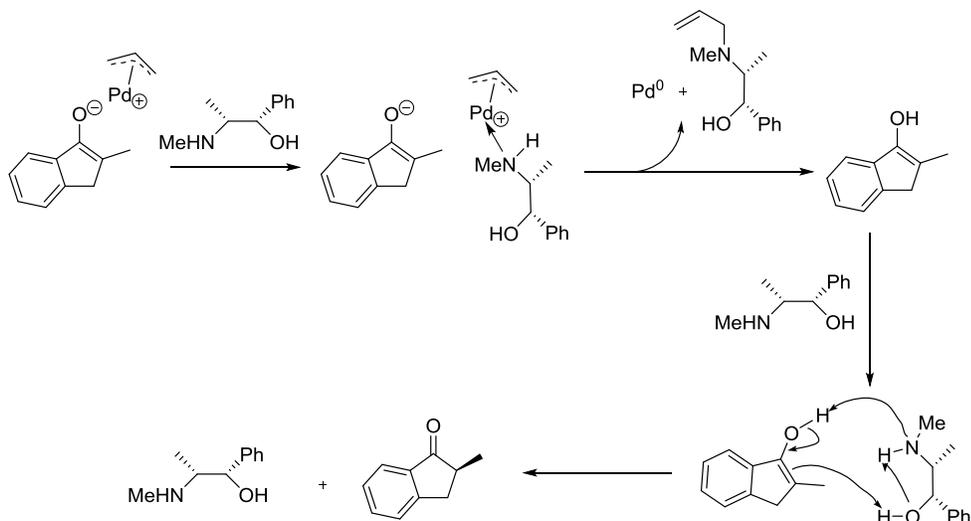
Figure 4.4. Tsuji's Pd-catalyzed decarboxylative protonation of mixed malonate esters.

Muzart reported a decarboxylative protonation methodology for allyl enol carbonates<sup>109</sup> and  $\beta$ -keto allyl esters<sup>110</sup> using ephedrine as a chiral proton source



Scheme 4.3. Muzart's enantioselective Pd-catalyzed decarboxylative protonation.

(Scheme 4.3). At least one equivalent of ephedrine was required in order to drive the reaction to completion. In the case of allyl enol carbonate, a yield of 90% was achieved, however a modest 38% ee was the highest enantioselectivity achieved. When  $\beta$ -keto allyl esters were employed, the highest ee (43%) was obtained with a yield of 62%. While it was possible to achieve a higher chemical yield, it came at the cost of enantioselectivity. The mechanism proposed by Muzart and co-workers is depicted in Scheme 4.2. The  $\pi$ -allyl palladium species is attacked by



Scheme 4.2. Muzart's proposed mechanism for enantioselective decarboxylative protonation.

nucleophilic ephedrine. The amine proton is delivered to the enolate to form the corresponding enol, while the ephedrine is allylated. It is envisioned that additional ephedrine would then promote an enantioselective tautomerization of the enol to give the enantioenriched product. This mechanism accounts for the fact that greater than one equivalent of ephedrine is required for the reaction to proceed to completion. Additionally, the allylated ephedrine species was isolated in 93% yield.

In 2006, Stoltz and co-workers were successful in adapting their palladium-catalyzed enantioselective decarboxylative allylation methodology to an enantioselective protonation.<sup>111</sup> The allylation methodology employed *t*-butyl PHOX ligand, along with Pd<sub>2</sub>(dba)<sub>3</sub> as the pre-catalyst. They envisioned that intercepting the palladium-bound enolate containing the chiral ligand with a proton source could yield the desired highly enantioenriched product (Figure 4.5). Using conditions similar to Tsuji's 1985 report, Stoltz and co-workers screened conditions using the phosphinooxazoline ligand. They found that the exclusion of amine base was helpful in increasing the ee. In an attempt to remove the small amounts of water that are present in commercially available formic acid they included

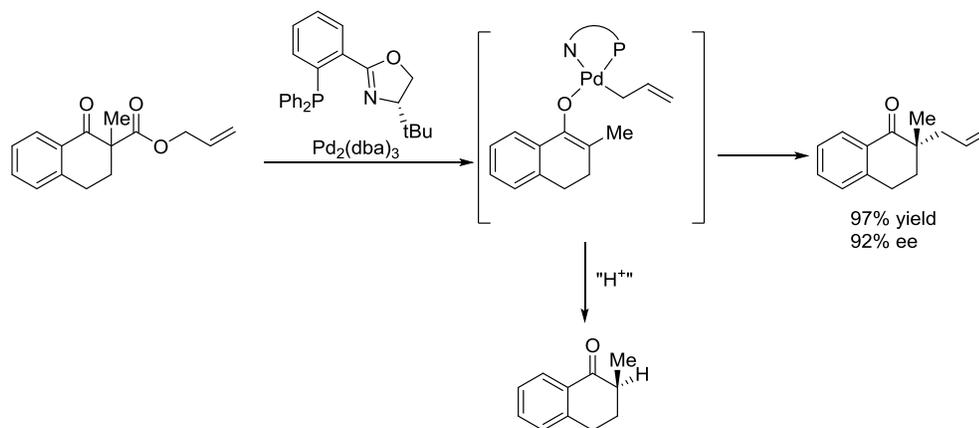


Figure 4.5. Stoltz's enantioselective Pd-catalyzed decarboxylative protonation.

molecular sieves in the reaction mixture and observed that this resulted in a dramatic increase in ee.

Selected examples from the substrate scope are shown in Table 4.1. The yields were good to excellent. The enantioselectivity is good for systems in which there exists some rigidity, such as fused ring systems containing an aromatic ring. However, the enantioselectivity is diminished in more flexible systems. Additionally, it was found that the reaction conditions had to be re-optimized for each substrate to obtain optimal results. It was hypothesized that the heterogeneous nature of the reaction conditions (molecular sieves and formic acid that is not fully soluble) may be contributing to the issues.

Table 4.1. Substrate scope of Stoltz's enantioselective protonation.

Substrate	Product	Time (h)	Isolated Yield (%)	ee (%)
		R = Me 10	88	94
		R = allyl 4	88	85
		R = F 5	79	88
		R = Me 5	91	95
		R = allyl 6	81	88
		R = Bn 5	95	78
		22	83	81
		n = 0, R = Bn 4	63	60
		n = 1, R = Me 4.5	99	85
		n = 2, R = Bn 4.5	91	92
		n = 2, R = Bn 5	69	74
		3	81	84

Deuterium-labelling experiments were undertaken by the Stoltz group in an attempt to further understand the mechanism. As shown in Figure 4.6, the decarboxylative protonation was performed with  $\text{HCO}_2\text{D}$ , under the optimized conditions. The initial hypothesis was that the formic acid was providing the proton source for the protonation. Despite extensive experimentation, the product of the labelling experiment was found to contain a maximum of 35% deuterium. Exhaustive drying of all reagents, with particular attention to the molecular sieves, did not improve the deuterium incorporation. The second experiment used  $\text{DCO}_2\text{H}$ , where the deuterium was located in the formyl moiety instead of the acid. The

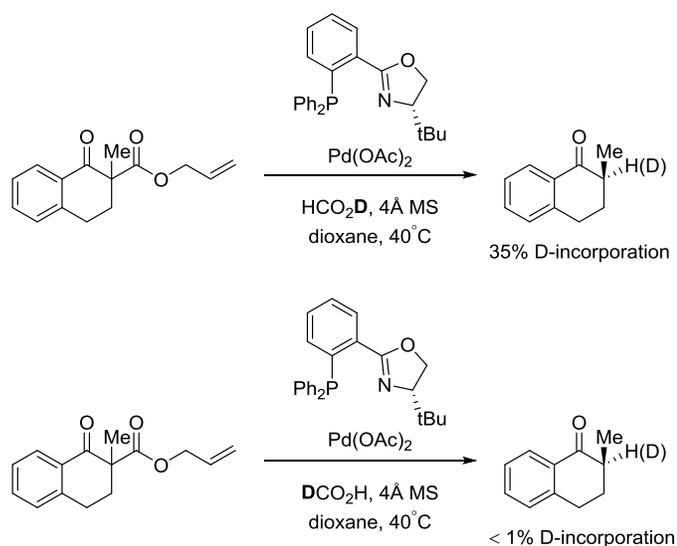


Figure 4.6. Labelling experiment in Stoltz's Pd-catalyzed decarboxylative protonation.

deuterium incorporation in the product was below the limit of detection. A control experiment, with fully unlabelled substrate and reagents, under identical conditions and scale to the D-incorporation experiments, also gave no deuterium incorporation. A footnote in the paper states, "The detailed mechanism of proton

incorporation (e.g. proton transfer, reductive elimination, or otherwise) remains unclear and is under investigation.”<sup>111</sup>

This methodology was expanded upon by evaluating fully soluble organic acids. Stoltz and his team found that the use of Meldrum's acid along with a Pd(0) precatalyst ( $\text{Pd}_2(\text{dba})_3$ ) gave comparable results.<sup>112</sup> The sense of enantioinduction was the same between the two systems, suggesting similar mechanisms. Intriguingly, up to 8 equivalents of formic acid were required to suppress the formation of the allylation product. In the case of the homogeneous conditions, no decarboxylative allylation was observed. However, the fate of the allyl group was notable: diallylated Meldrum's acid was isolated as a byproduct

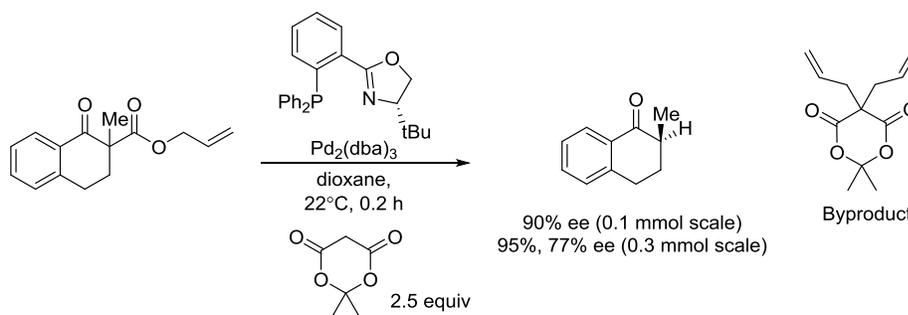
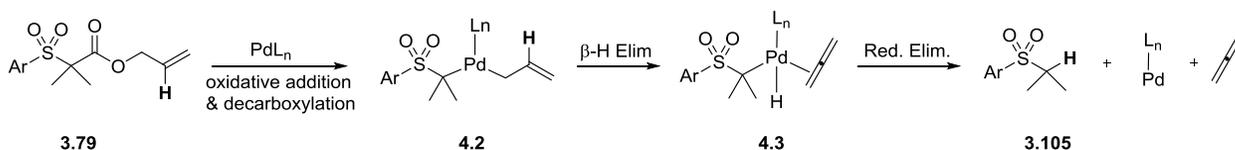


Figure 4.7. Homogeneous Pd-catalyzed decarboxylative protonation.

(Figure 4.7). Monoallylated Meldrum's acid was never observed. To evaluate the kinetics of the enantioselective protonation, the disappearance of the allyl ester was monitored by  $^1\text{H}$  NMR in  $\text{C}_6\text{D}_6$ . A zero-order decay is observed, suggesting that the allylic ester reacts very quickly to produce an intermediate that then proceeds to the product via a slower step.

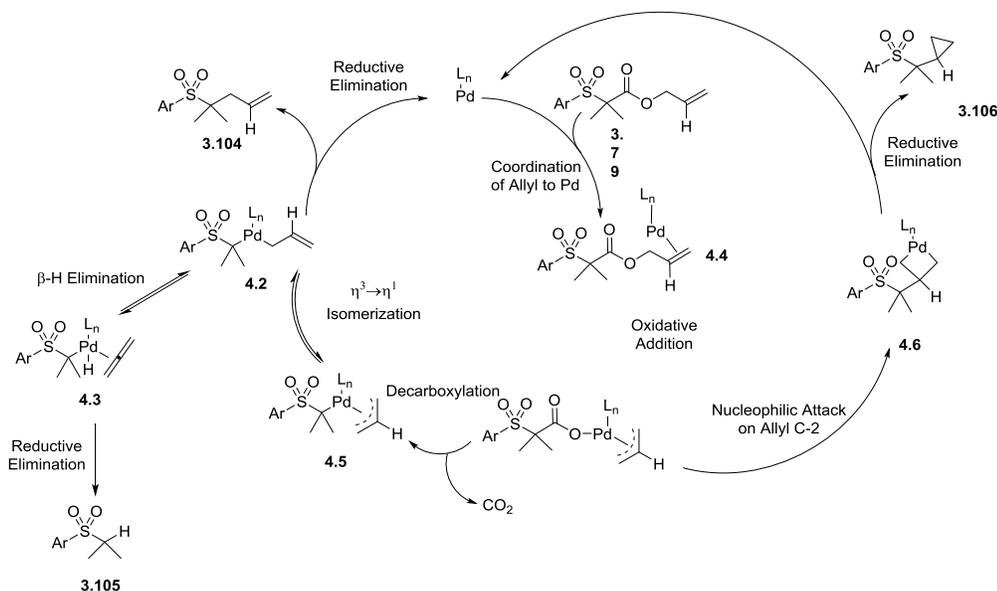
## 4.2.2 Allene Proposal

Our initial mechanistic proposal involved a  $\beta$ -hydride elimination from the  $\eta^1$ -bound allyl to form a palladium hydride species and an allene (which may or



Scheme 4.4. Proposed mechanism accounting for formation of protonated product.

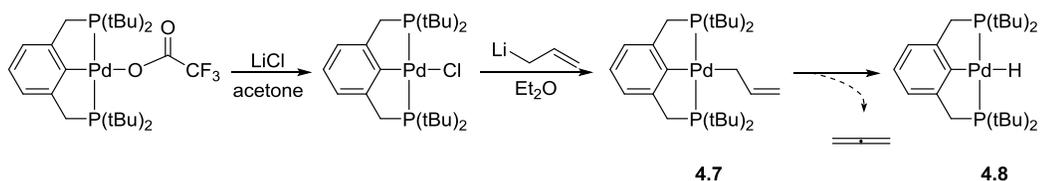
may not be bound to the Pd center) (Scheme 4.5, Scheme 4.4). Subsequent reductive elimination of the alkyl sulfone and hydride would yield the protonated product and regenerate the Pd(0) catalyst. While the chemistry of palladium



Scheme 4.5. Proposed catalytic cycle accounting for protonated & cyclopropanated products.

hydrides and palladium allene species is quite rich, examples of a  $\beta$ -hydride elimination from an allyl onto palladium are scarce in the literature. The only example found was from Wendt and co-workers from their report on the preparation of a thermally unstable  $\eta^1$ -allyl palladium pincer complex (Scheme

4.6).<sup>113</sup> The decomposition product was the corresponding palladium hydride species, observed spectroscopically by <sup>31</sup>P and <sup>1</sup>H NMR. The <sup>1</sup>H NMR was particularly informative; a triplet at -3.73 ppm was observed. The authors hypothesized that the product was the result of a β-hydride elimination to form allene, although they are careful to note that no allene was ever detected. Other possible mechanisms could not be ruled out.



*Scheme 4.6. Wendt's synthesis of allyl Pd-pincer complexes.*

We chose to evaluate this mechanistic proposal through the use of deuterium labelled substrates. The initial targets were a substrate with a deuterium in the C-2 position of the allyl group, as well as a substrate with deuterium in the C-1 position. According to the mechanistic proposal, it would be expected that high deuterium incorporation would be observed in the product from the C-2 labelled substrate (Figure 4.8, top). Likewise, low or zero deuterium incorporation would be expected in the product from the C-1 labelled substrate (Figure 4.8, bottom).

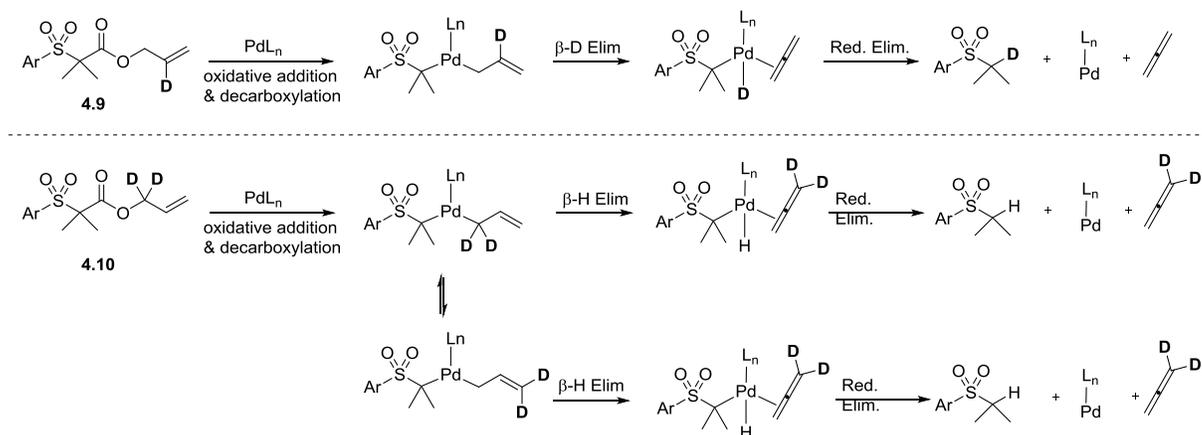


Figure 4.8. Expected label distribution based on mechanistic proposal.

### 4.2.3 Preparation of Deuterium Labelled Substrates

The requisite allyl-2-*d* alcohol was prepared via a deuterioaluminum of propargyl alcohol with lithium aluminum deuteride (Figure 4.9).<sup>114</sup> The labelled allylic alcohol was then subjected to the optimized synthetic sequence for preparation of substrates. A small amount of over-reduced product (determined to be *n*-propyl-2-*d*<sub>2</sub> alcohol) was obtained during the initial deuterium incorporation. It was not practical to separate this material and was thus carried through the entire

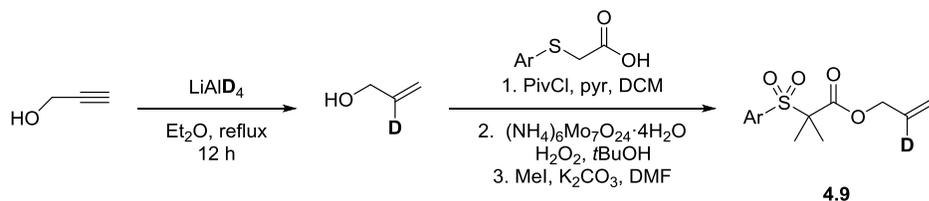


Figure 4.9. Synthesis of allyl-2-*d* mechanistic probe.

previously optimized synthetic sequence to  $\alpha,\alpha$ -dialkylated BTMP sulfone allyl esters. The requisite allyl-1,1-*d*<sub>2</sub> alcohol was prepared according to a literature

procedure via lithium aluminum deuteride reduction of acryloyl chloride (Figure 4.10).<sup>115</sup> The labelled alcohol was then esterified, oxidized and alkylated according to the optimized procedure.

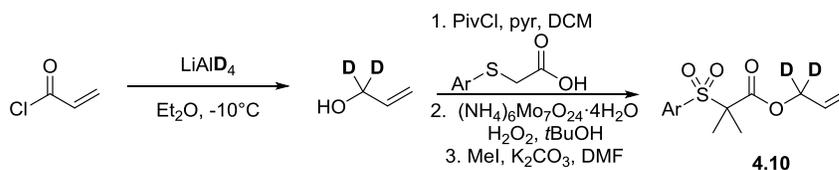


Figure 4.10. Synthesis of allyl-1,1- $d_2$  mechanistic probe.

#### 4.2.4 Results of DcA on Isotopically Labelled Substrates

The initial mechanistic studies took place prior to the determination of the issues associated with  $\text{Pd}_2(\text{dba})_3$ . The best results with the  $\alpha,\alpha$ -dimethyl substrate were obtained using BINAP in THF at room temperature. These conditions were applied to the allyl-2- $d$  dimethyl substrate. As expected, a mixture of allylated, cyclopropanated and protonated product was produced (Figure 4.11). The products were separated by flash column chromatography and analyzed by  $^1\text{H}$  NMR. The allylated product retained the deuterium label in the 2 position; the cyclopropyl product also retained the deuterium label in the 2 position. The protonated product, however, was obtained as a mixture of protonated and deuterated products, in an 85.5 : 14.5 ratio (determined by integration of  $^1\text{H}$  NMR peaks in the aromatic region and comparing with the integration of the proton adjacent to two methyl groups, appearing as a septet).

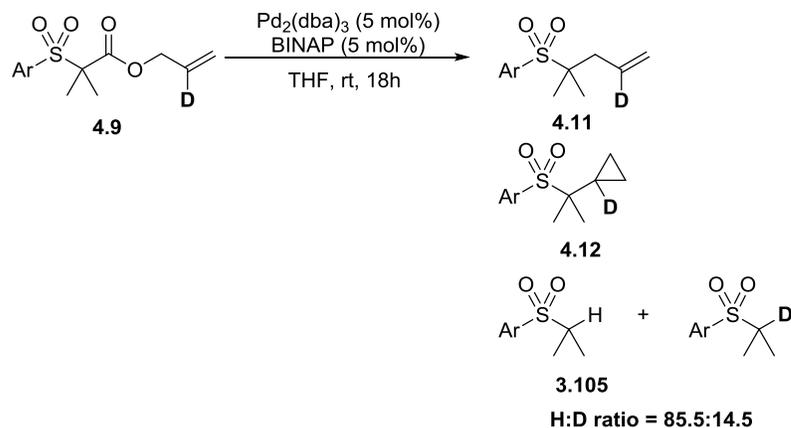


Figure 4.11. Results of allyl 2-d mechanistic probe.

The allyl-1,1- $d_2$  mechanistic probe was subjected to identical reaction conditions. The results are summarized in Figure 4.12. The allylated product was a 1:1 mixture of 1,1- $d_2$  and 3,3- $d_2$  allyl groups. This is reasonable given that the  $\eta^1 \rightarrow \eta^3 \rightarrow \eta^1$  isomerization of an allyl group bound to palladium is very rapid. The cyclopropyl product appeared to have D-labels on a single carbon.  $^1\text{H}$  NMR analysis of the protonated product indicated a small amount of D-incorporation, in a ratio of 96.7 : 3.3.

The results of both experiments are inconsistent with the proposed mechanism. One would expect complete deuterium incorporation in the protonated product in the case of the allyl-2- $d$  probe and zero deuterium incorporation for the allyl-1,1- $d_2$  probe. The fact that there was some deuterium incorporation in the case of the allyl-2- $d$  probe was quite interesting, though. We considered that the proposed mechanism was not entirely wrong, but that there was a competitive process occurring.

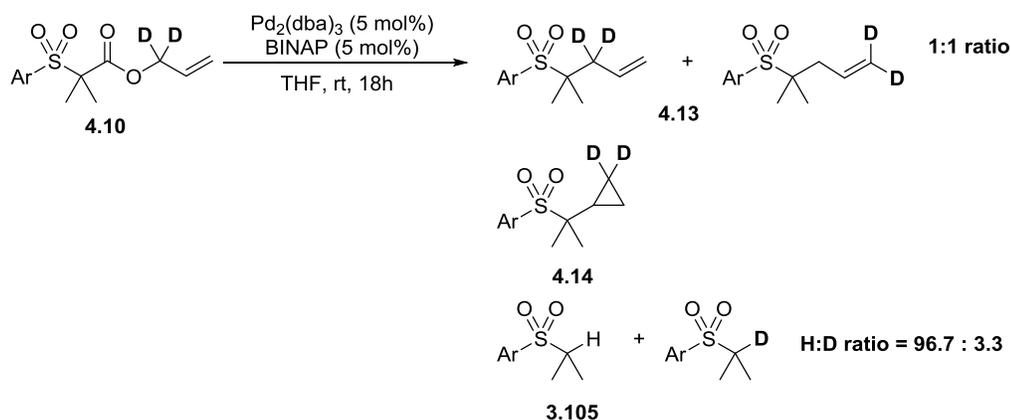


Figure 4.12. Results of allyl-1,1- $d_2$  mechanistic probe.

## 4.2.5 Revised Mechanistic Proposal

Yoshinori Yamamoto and co-workers reported on the Pd-catalyzed addition of  $\alpha$ -methyl malononitrile derivatives to allenes.<sup>116–118</sup> This process was termed hydrocarboxylation. Electronic effects in the substrate had a profound impact on the

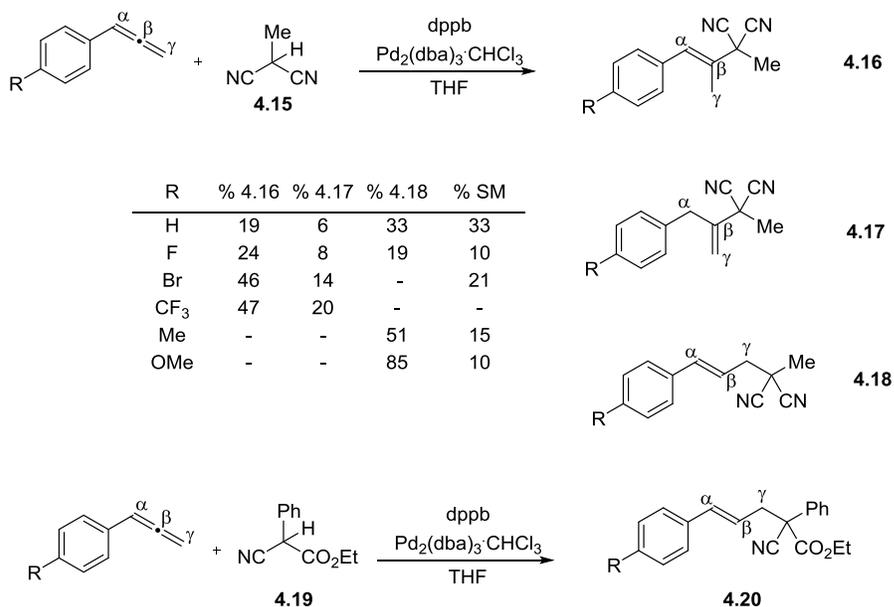


Figure 4.13. Yamamoto's Pd-catalyzed hydrocarboxylation of allenes.

product distribution. Relatively electron-rich substrates gave predominantly

addition to the terminal ( $\gamma$ ) carbon of the allene, while more electron-poor substrates yielded addition products to the internal ( $\beta$ ) carbon of the allene (Figure 4.13). The use of the more sterically demanding ethyl  $\alpha$ -phenylcyanoacetate gave terminal addition products exclusively. Yamamoto considered two different mechanistic rationalizations for the observed results. As illustrated in Figure 4.14, the allene may undergo hydropalladation such that the hydride is added to the  $\gamma$  position, resulting in a vinylic palladium species. Alternatively, a carbopalladation may take place, yielding an  $\eta^3$ -allyl bound Pd-H species.

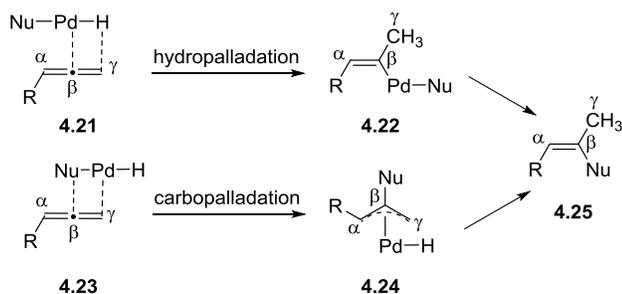


Figure 4.14. Yamamoto's mechanistic proposals for hydrocarbonation of allenes.

It was hypothesized that the proposed palladium-hydride intermediate may undergo a reversible carbopalladation/ $\beta$ -hydride elimination process, as shown in Figure 4.15, in which a vinylic palladium intermediate is formed. The distribution of the isotopic label in the protonated product may be explained by considering that the reductive elimination step may be influenced by a kinetic isotope effect.

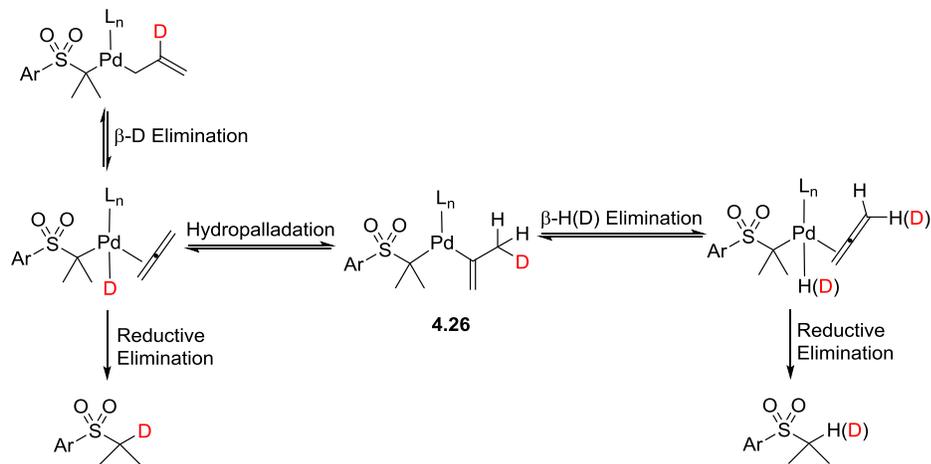
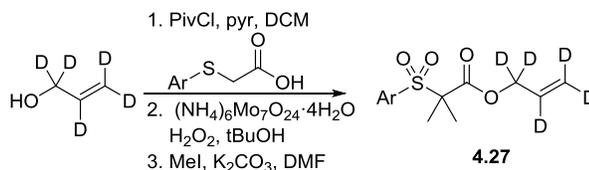


Figure 4.15. Revised mechanistic proposal for generation of protonated product.

To evaluate this proposal, a perdeuterated allyl mechanistic probe was prepared from commercially available allyl-1,1,2,3,3- $d_5$  alcohol via the standard procedure (Scheme 4.7).



Scheme 4.7. Synthesis of allyl-1,1,2,3,3- $d_5$  mechanistic probe.

#### 4.2.6 DcA Reactions on Mechanistic Probes with Baird Catalyst

The two previous experiments using isotopically labelled substrates were repeated using the newly optimized reaction conditions using the Baird catalyst. The best results with the  $\alpha,\alpha$ -dimethyl substrate was using  $\text{PPh}_3$  as ligand. The results are summarized in the following sections.

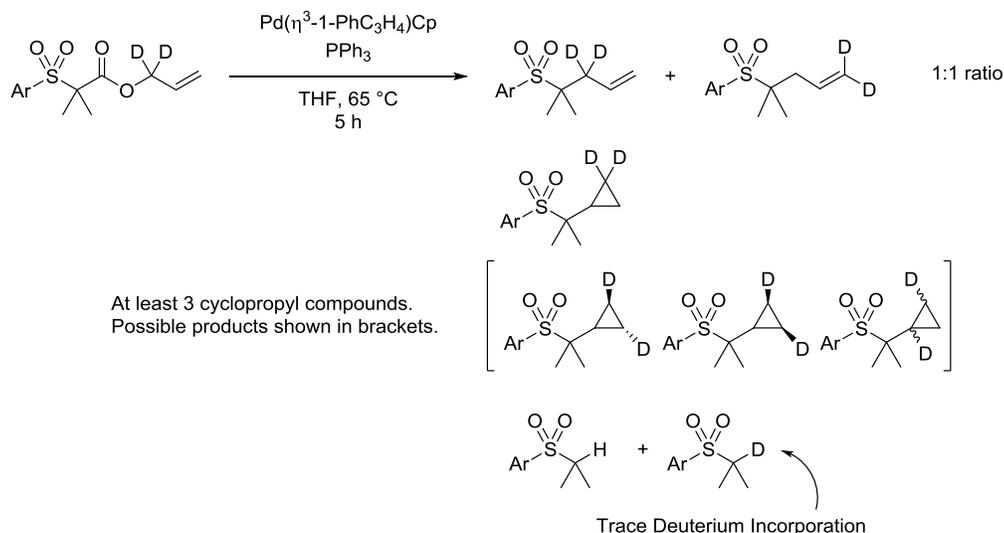


Figure 4.16. Results of allyl-1,1-d<sub>2</sub> mechanistic probe with Baird catalyst.

Exposure of the allyl-1,1-d<sub>2</sub> mechanistic probe to the DcA conditions resulted in the formation of allylated, protonated and cyclopropanated products. The allylated products were isolated as a 1:1 mixture of isotopic regioisomers, as is typically observed due to rapid isomerization of the allyl group. The main cyclopropyl product isolated is shown in Figure 4.16, but other isotopic regioisomers were present. The identification of these other cyclopropyl products is not trivial and work is ongoing to characterize them. The protonated product contained a trace amount of deuterium incorporation.

The identical reaction with the allyl-2-d mechanistic probe also gave allylated, protonated and cyclopropanated, as expected (Figure 4.17). Interestingly, the deuterium incorporation at the C-2 position in the allylated product had decreased by 7% in comparison to the starting material. The cyclopropanated product appeared to be a single isotopic regioisomer. The protonated material contained only a small amount of deuterium.

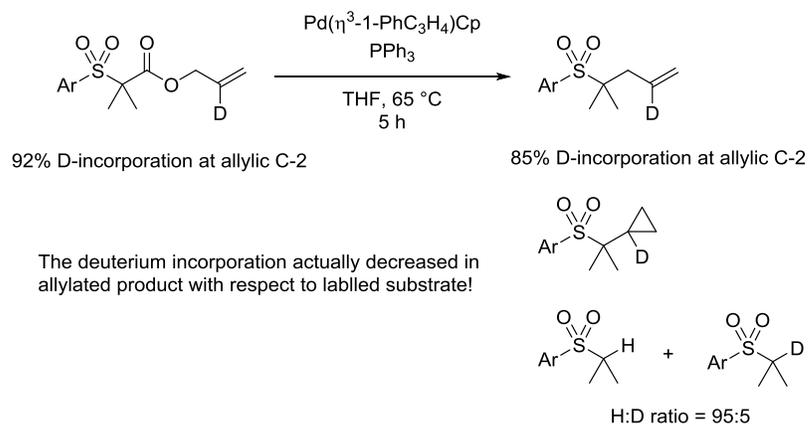


Figure 4.17. Results of allyl-2-d mechanistic probe with Baird catalyst.

The identical reaction on the perdeuterated substrate yielded the expected products, as illustrated in Figure 4.18. The isolated allylated product didn't appear to have lost any deuterium labels. The cyclopropanated product appeared to have multiple isotopic regioisomers that remain unidentified. Most importantly, however, the protonated product contained less than 5% deuterium incorporation. Although we haven't conclusively discounted the allene mechanistic proposal, it certainly is not a dominant pathway.

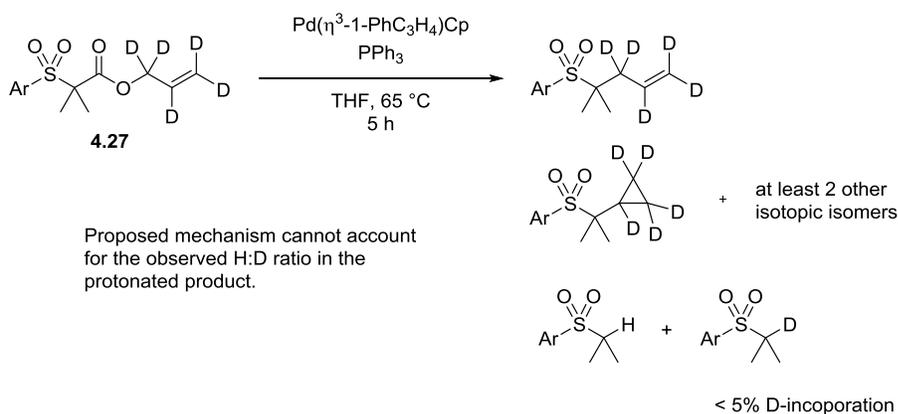
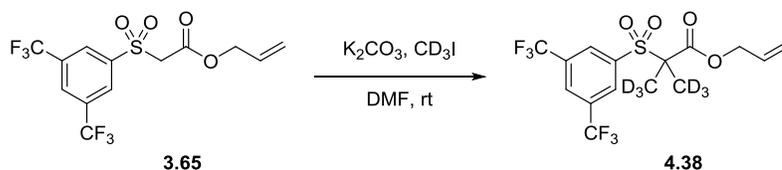


Figure 4.18. Results of allyl-1,1,2,3,3-d<sub>5</sub> mechanistic probe with Baird catalyst

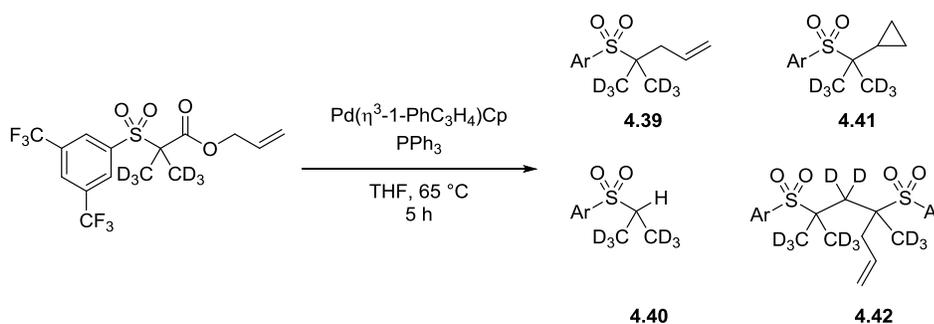
### 4.2.7 Synthesis and Evaluation of $\alpha,\alpha$ -dimethyl- $d_3$ Mechanistic Probe

We elected to also synthesize a mechanistic probe in which the alkyl groups in the  $\alpha$ -position were deuterium-labelled. Starting from sulfone shown in Scheme 4.8, the isotopically labelled  $\alpha,\alpha$ -dimethyl substrate was prepared via the standard alkylation procedure (Scheme 4.8). Since the isotopic label is introduced in the last step of the substrate sequence, a larger amount of substrate was able to be easily and efficiently prepared. Treatment of this substrate with Baird catalyst and  $\text{PPh}_3$



Scheme 4.8. Synthesis of  $\alpha,\alpha$ -dimethyl- $d_3$  mechanistic probe.

in THF at  $65^\circ\text{C}$  for 5 hours resulted in complete consumption of starting material and production of 4 products (Scheme 4.9). The corresponding allylated **4.39**, protonated **4.40**, cyclopropanated **4.41** and dimeric product **4.42** were formed and isolated via column chromatography.



Scheme 4.9. Results of  $\alpha,\alpha$ -dimethyl- $d_3$  mechanistic probe.

#### 4.2.8 Summary

Although small amounts of deuterium incorporation were observed in the protonated products isolated from these mechanistic experiments, the proposed mechanism could not account for the origin of the majority of the protonated product. Alternate mechanistic considerations were required.

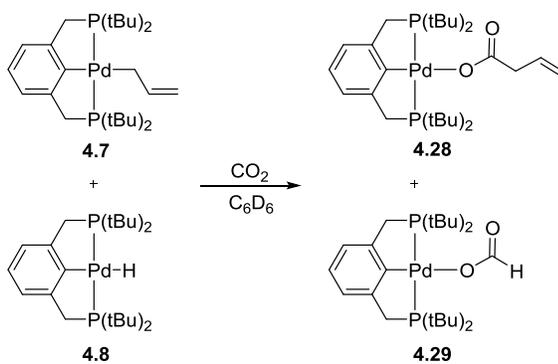
#### 4.3 Palladium (I) Dimers and Carboxylation

Transition metal catalyzed reduction of carbon dioxide has become a popular topic of study in recent years. The use of CO<sub>2</sub> as a feedstock to higher molecular weight, value-added products is extremely attractive. In the context of the ongoing mechanistic investigations in our lab, reports from two research groups in this area caught our attention.

The work from the lab of Ola Wendt was previously discussed in Scheme 4.6 with respect to their mechanistic proposal that an  $\eta^1$ -allyl palladium pincer complex might undergo a  $\beta$ -hydride elimination to yield the corresponding palladium hydride complex. The  $\eta^1$ -allyl palladium pincer complex could never be completely purified; there was always some of the palladium hydride complex. The intended application of the allyl palladium pincer complex was for activation of CO<sub>2</sub>. Wendt had previously developed analogous methyl palladium pincer complexes and found that exposure to CO<sub>2</sub> resulted in the corresponding acetate compound.<sup>119</sup>

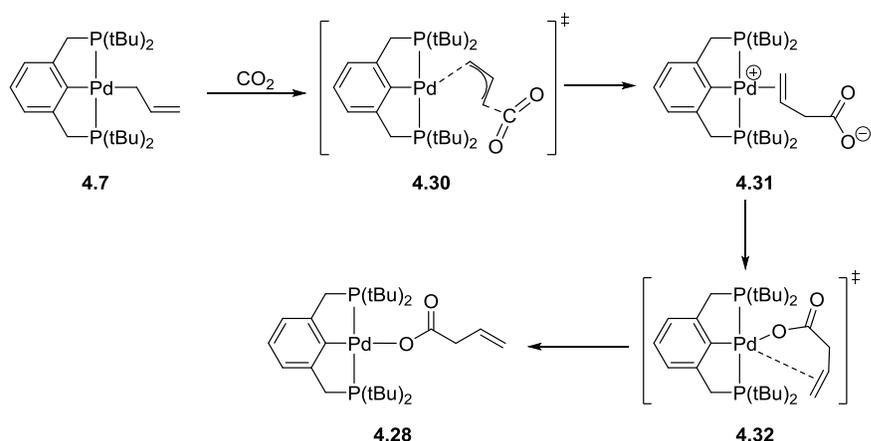
In the allyl work, a mixture of  $\eta^1$ -allyl palladium pincer complex and the corresponding hydride compound were treated with approximately 4 atm of CO<sub>2</sub>. The reaction was complete within several minutes. The major product was

identified as the butenoate-bound complex, while the minor product was inferred to be the corresponding formyl-bound complex (Scheme 4.10). This inference is substantiated by the presence of a triplet at  $\delta$  9.08 ( $J_{\text{PH}} = 1.65$  Hz), which is consistent with a formate proton. The authors noted that the rate of reaction for the allyl complex was several orders of magnitude faster than the carboxylation of the methyl complexes.



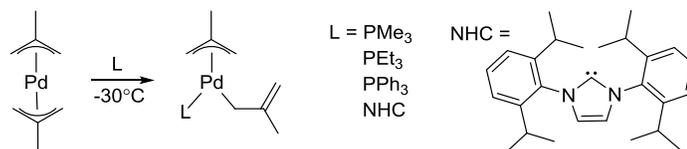
Scheme 4.10. Wendt's carboxylation of allyl Pd-pincer complexes.

In 2010, Wendt and co-workers published a follow-up mechanistic study. DFT calculations supported a two-step mechanism (Scheme 4.11). In the first step, the nucleophilic terminus of the alkene attacks the electrophilic carbon dioxide. A zwitterionic intermediate is formed as a result, with a cationic palladium center and a negatively charged carboxylate terminus. This intermediate then rearranges to form the carboxylate-bound final product. Other modes of reaction for  $\text{CO}_2$  were evaluated concurrently, including modes in which  $\text{CO}_2$  initially coordinates to the metal center, however this mechanism gave the lowest enthalpy pathway.



*Scheme 4.11. Wendt's mechanistic proposal for carboxylation of allyl Pd-pincer*

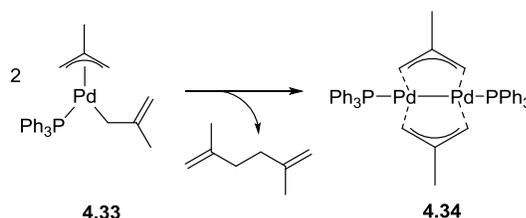
Also in 2010, Hazari and co-workers reported on an interesting series of allyl-bound palladium complexes. Treatment of bis(methallyl)palladium with a variety of phosphine ligands, as well as an NHC ligand, resulted in palladium complexes with one allyl group  $\eta^3$  coordinated, and the other allyl group  $\eta^1$  coordinated (Figure 4.19).<sup>120</sup> In solution, the allyl groups show fluxional behavior;



*Figure 4.19. Preparation of mixed  $\eta^1$  and  $\eta^3$ -allyl Pd complexes by Hazari.*

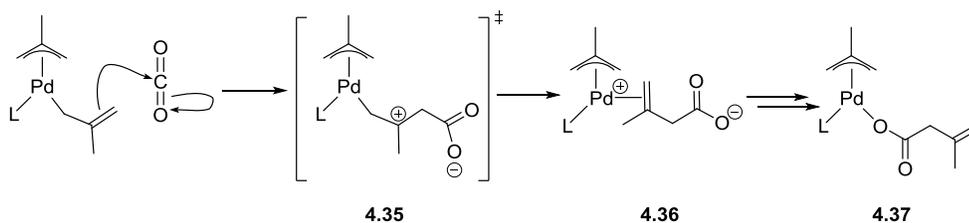
this is easily observed by <sup>1</sup>H NMR. It was possible, however, to differentiate between the allyl groups by NMR at low temperature. X-ray crystallography was performed on a crystal grown of the PPh<sub>3</sub> analogue. The bond lengths observed were consistent with two different modes of allyl coordination. This represented the first example of structural characterization of a compound with two different binding modes for allyl fragments.

When this series of compounds was reacted with excess CO<sub>2</sub>, rapid and quantitative formation of the corresponding carboxylate compounds was observed. Those compounds with phosphine ligands reacted in about 1 h at -20 °C, while the compound with the NHC ligand reacted in less than 5 minutes at -40 °C. These compounds were exceptionally reactive with CO<sub>2</sub>, however they were also thermally unstable. The PPh<sub>3</sub> analogue was found to cleanly react to give one equivalent of 2,5-dimethylhexa-1,5-diene and the dimeric bridging 2-methylallyl Pd(I) species (Scheme 4.12).



Scheme 4.12. Proposed pathway for thermal degradation to Pd(I) dimer.

Hazari and co-workers also studied the carboxylation of the 2-methylallyl compounds by DFT and obtained results similar to that reported by Wendt.<sup>120</sup> The data suggested a zwitterionic transition state that subsequently collapses to a cationic palladium species with a bound carboxylate ligand (Scheme 4.13). Ligand exchange forms the final product in which the carboxylate is bound to palladium through oxygen.



Scheme 4.13. Mechanistic proposal for carboxylation from Hazari.

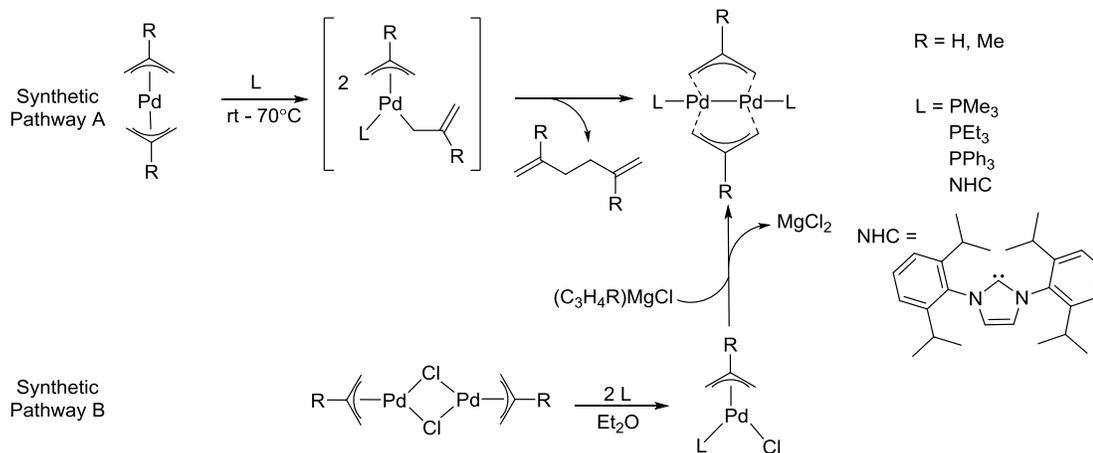


Figure 4.21. Improved synthesis of Pd(I) dimers.

Hazari and co-workers then followed up with an improved ligand synthesis.<sup>121</sup> Although initial pathway (shown as Pathway A, Figure 4.21) was efficient and high yielding, the preparation of the thermally unstable bis(allyl) palladium starting materials was tedious. A much improved, two-step process was developed. Treatment of the allylic palladium chloride dimer with 2 equivalents of the appropriate ligand in  $\text{Et}_2\text{O}$  gives the Pd(II) monomer shown. This intermediate is then treated with the appropriate allylic Grignard reagent, forming the desired Pd(I) dimer. The chloride intermediate may be isolated or the entire process may be carried out in a single pot operation. A series of Pd(I) dimers were prepared and evaluated for their ability to react with carbon dioxide. The corresponding bridging carboxylates were formed in high yield (Figure 4.20). This reaction was

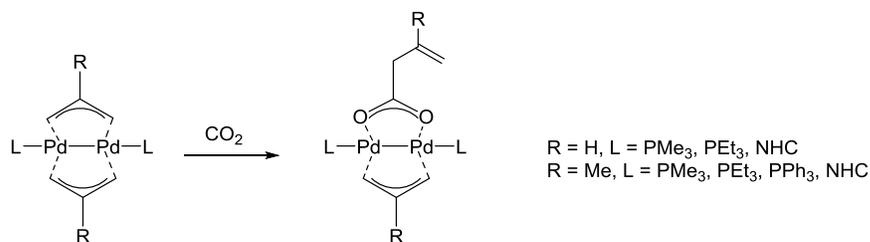


Figure 4.20. Carboxylation of Pd(I) dimers.

found to be irreversible. Treatment of the bridging carboxylates with  $^{13}\text{C}$ -labelled  $\text{CO}_2$  gave zero incorporation of the isotopic label.

#### 4.4 Ligand C-H Activation Proposal

Having exhausted all allylic positions as well as the  $\alpha,\alpha$ -dialkyl groups as possible sites of origin for the proton, we began to consider that perhaps the ligand was the source. Although the idea seemed unlikely at first, examination of the literature revealed several examples that legitimized the concept.

While investigating the synthesis and reactivity of palladium carbonyl clusters, Moisev and co-workers made an interesting observation. Treatment tetranuclear palladium cluster with 1,10-phenanthroline ligand formed the corresponding cluster (Figure 4.22). However, if one started from the much simpler palladium (II) acetate starting material, and attempted to prepare the desired palladium cluster compound in one step, a different compound was formed. Notably, the  $^1\text{H}$  NMR spectrum of this compound displayed a singlet at -15.8 ppm. This extremely shielded chemical shift is consistent with a hydride bound to palladium.

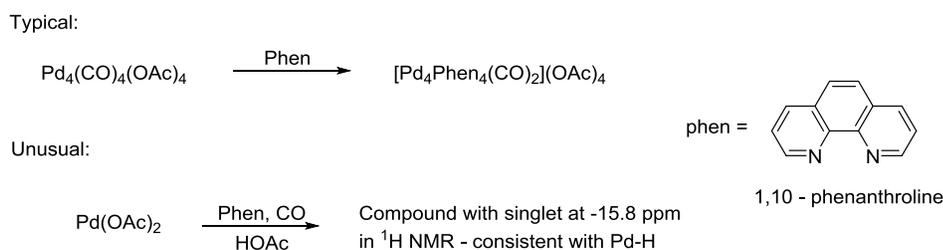


Figure 4.22. Moisev's synthesis of Pd cluster compounds.

The authors considered the possibility that the origin of the hydride was the acetic acid. Conceivably, oxidative addition of acetic acid to the palladium (0)



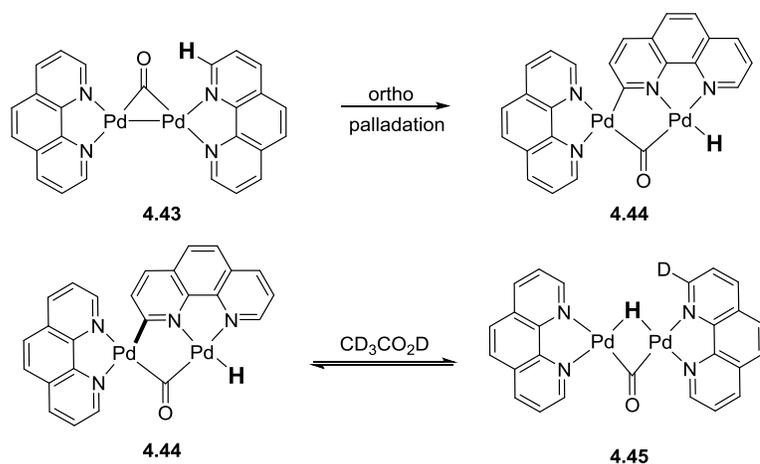
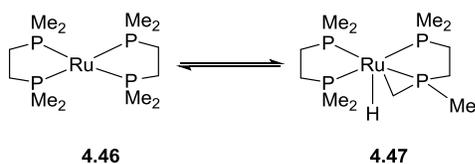


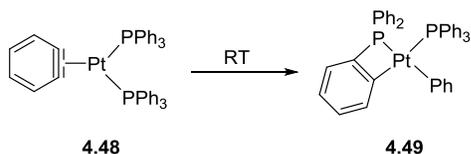
Figure 4.24. Ortho-palladation of phenanthroline ligand.

We then examined the literature for examples of metalation of tertiary phosphine ligands. The first example of such a process was reported by Chatt and Davidson in 1965.<sup>122</sup> This ground breaking study revealed a tautomeric equilibrium between the two complexes shown in Scheme 4.14. Detailed deuterium labelling studies proved that the origin of the metal hydride was from one of the methyl groups in the tertiary phosphine ligand. Although the metal hydride complex is reactive and was shown to reduce bromoethane to ethane, the Ru(0) complex was hypothesized to be more reactive, thus shifting the equilibrium towards the non-metalated complex.



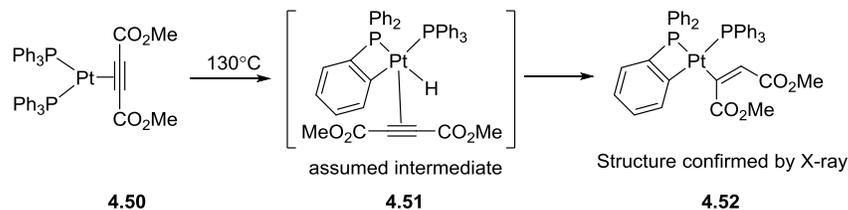
Scheme 4.14. Tautomeric equilibrium in Ru complexes with tertiary phosphine ligands.

Since that initial report, there have been many examples of cyclometalated transition metal complexes containing tertiary phosphines. These were reviewed at length by Mohr and Bennett in 2006.<sup>123</sup> Examples involving the Ni, Pd, Pt triad of the periodic table, however, are largely limited to Pt. Clark and Hine found that



*Scheme 4.15. Facile ortho-platination from benzyne-Pt complex.*

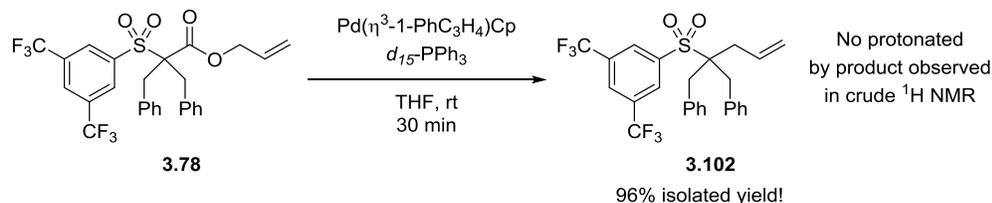
heating a solution of the dimethyl acetylenedicarboxylate platinum (0) complex in toluene for 24 h yielded the *ortho*-platinated complex of triphenylphosphine (Scheme 4.16).<sup>124</sup> This structure was confirmed several years later by X-ray crystallography performed by Oliver and co-workers.<sup>125</sup> The mechanism is presumed to involve to formation of the Pt-H bond by cycloplatination of triphenylphosphine, followed by insertion of the alkyne. Bennett and co-workers have reported substantial work in the area of cyclometalated complexes. The scheme below shows a relatively facile cyclometalation that occurs from a platinum (0) complex with a  $\eta^2$ -coordinated benzyne (Scheme 4.15).



*Scheme 4.16. ortho-platination of triphenylphosphine.*

#### 4.4.1 Use of $d_{15}$ -PPh<sub>3</sub> on unlabelled substrate

The theory of a ligand C-H activation pathway from tertiary phosphines was evaluated using the  $\alpha,\alpha$ -dibenzyl BTMP sulfone allyl ester as a test substrate (Scheme 4.17). We elected to run the reaction at room temperature to promote protonation, if possible. Remarkably, analysis of the crude material by <sup>1</sup>H NMR



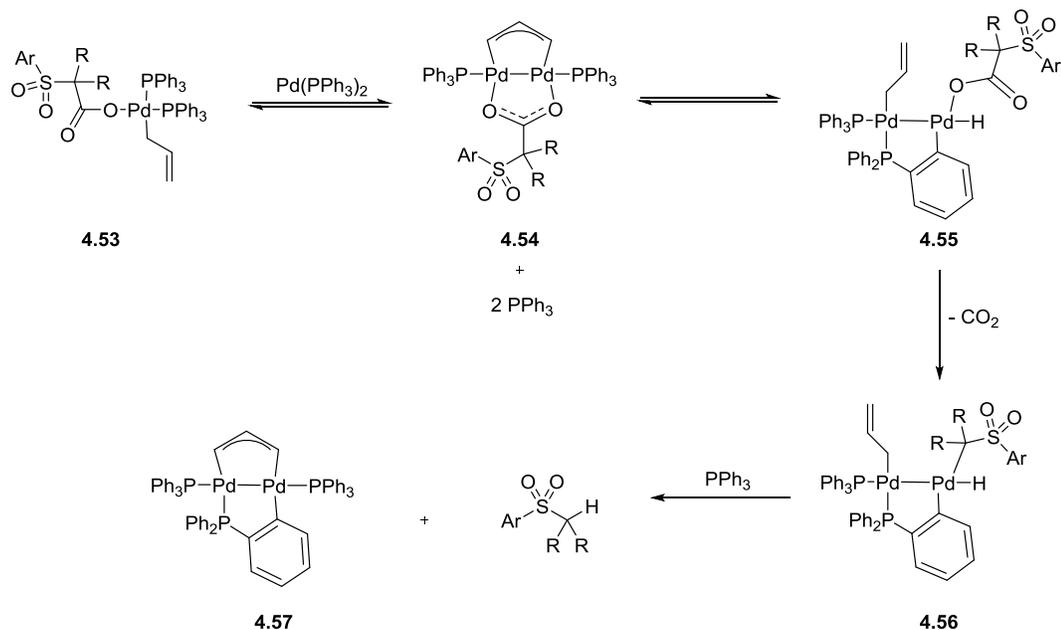
showed no trace of protonated (or deuterated) product. In fact, the homoallylic sulfone was isolated in a 96% isolated yield! This high of yield had never been obtained using BTMP sulfones.

The inhibition of the protonated product is indirect evidence of a mechanistic pathway involving metalation of the ligand. The use of  $d_{15}$ -PPh<sub>3</sub> likely produced a kinetic isotope effect such that the rate of allylation was faster than the rate of protonation. When mixtures of allylated and protonated products are obtained, the rates for the pathways must be similar.

#### 4.4.2 Proposed Mechanism

Starting from a structure similar to that identified by Stoltz as the resting state of the palladium catalyzed DcA reaction, with an *O*-bound carboxylate and an  $\eta^1$ -coordinated allyl fragment, one could envision association with addition  $\text{Pd}(\text{PPh}_3)_2$  to form a Pd(I) dimer, similar to those reported by Hazari (Scheme 4.18).

Allylic Pd(I) dimers have also been reported by Koningsberger<sup>126</sup> and were implicated by Pfaltz in the mechanism of Pd-catalyzed allylic substitution.<sup>127</sup> Intramolecular C-H activation of one of the benzene rings on triphenylphosphine results in a Pd hydride species, as well as a 5-membered bis-palladacycle **4.55**. Decarboxylation yields an alkyl palladium species **4.56**, which can then reductively eliminate to form the protonated product and **4.57**. Although **4.55** and **4.56** invoke a Pd(III) intermediate, these are hypothetical only and there is no experimental evidence to support this. Pd(III) intermediates, however, are not unknown in catalysis.<sup>128</sup> It is not clear if **4.57** could then act as a catalyst for the DcA reaction, although there are several well-known cyclopalladated pre-catalysts in the literature.<sup>129</sup>



Scheme 4.18. Proposed mechanism accounting for origin of protonated product.

#### 4.4.3 Implications of Proposed Mechanism

As far as we are able to ascertain, this type of mechanism has not been previously proposed in DcA or any other type of Pd-catalyzed reaction. There is some evidence that this proposed mechanism might extend beyond the BTMP sulfones. In Stoltz's decarboxylative protonation process, they were never able to incorporate more than 35% deuterium in the  $\alpha$ -position when using labelled formic acid. If we consider that a cyclometalated palladium hydride species is forming (similar to **4.55**), that intermediate could be stabilized by the presence of acid. An equilibrium with formic acid could be set up, similar to what was observed by Moissev in Figure 4.24. This accounts for only a fraction of the expected deuterium incorporation in the products.

This potential cyclopalladation has implications with many other commonly employed tertiary phosphine ligands. Widely used ligands, such as BINAP, BIPHEP, XANTPHOS, PHOX and DACH, all use an RPPH<sub>2</sub> motif. It is conceivable that the same type of cyclopalladation could occur with those ligands as well. It should be noted that this has not been demonstrated experimentally. Catalytic processes in which the cyclopalladation process is competitive with the desired pathway, use of d<sub>15</sub>-PPh<sub>3</sub> or other derivatives may be helpful in suppressing the apparent protodemetalation and subsequent protonation.

Currently, it is not well-understood why the protodemetalation/protonation process dominates in the DcA reaction for BTMP sulfones, and especially for the dimethyl-based substrates. The competitive processes may have become quite obvious due to the relatively high reactivity of the BTMP sulfones and the apparent

ease with which the competitive, undesired pathway can occur. The fact that protonation can be minimized by raising the temperature suggests that this may be a thermodynamically controlled process. For substrates such as Tunge's phenyl sulfones, the use of 95 °C temperature may help drive the equilibrium towards allylated product.

#### **4.5 Thesis Conclusions**

Triflone-based substrates with  $\alpha,\alpha$ -dialkylation are highly reactive in DcA processes, however their preparation is challenging. The change in electron withdrawing group to the BTMP sulfone facilitated the synthesis of a family of substrates. The substrate scope of the BTMP sulfones was quite good, although  $\alpha,\alpha$ -dimethyl substrates were stubbornly unreactive or gave unusual product distributions; the first example of a cyclopropane product from intramolecular DcA is reported, as well as a previously unreported dimeric product. The mechanistic studies that were undertaken have shown that the proton in the undesired protonated product is not due to C-H activation in the allyl fragment, nor from the  $\alpha,\alpha$ -dialkylation, at least in large part. Small amounts of deuterium incorporation were observed when allyl C-1 labelled compounds were used. The use of  $d_{15}$ -PPh<sub>3</sub> completely suppressed the formation of the protonation product and gave the allylated product in high yield. A mechanism involving a cyclopalladation of the ligand is proposed.

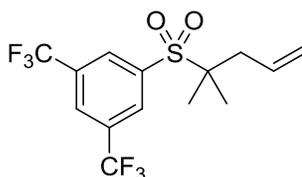
## 4.6 Experimental

### General

All reagents were purchased from commercial sources and were used as received, without further purification, unless otherwise noted. DCM, toluene, Et<sub>2</sub>O, were distilled from CaH<sub>2</sub> immediately prior to use. Tetrahydrofuran was distilled from lithium aluminum hydride or sodium/benzophenone prior to use. Reactions were monitored by thin-layer chromatography (TLC) using glass-backed extra hard layer (60 Å) TLC plates from Silicycle and visualized by fluorescence quenching under ultraviolet (UV) light and/or staining using potassium permanganate or ceric ammonium nitrate. Microwave heating was performed in glass vials (crimp-sealed with a septum liner and a metal fastener) in a Biotage Initiator 2.5 instrument with the absorption level set to “normal”. 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 Still *et al.*<sup>68</sup> or by automated chromatography on a Biotage Isolera One equipped with a UV detector. Concentration in vacuo refers to rotary evaporation with a 40 °C water bath at the appropriate pressure for the given solvent. Yields refer to purified and spectroscopically pure compounds unless indicated as crude. NMR spectra were recorded on a Bruker Avance III 300 or Bruker AMX 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm). Spectra are referenced to the internal standard tetramethylsilane (TMS) (0.00 ppm). <sup>19</sup>F NMR spectra are referenced to trifluorotoluene (- 63.7 ppm). Deuterium isotope effects are reported for <sup>13</sup>C NMR spectra of isotopically labelled compounds in comparison to their unlabelled counterparts. Infrared (IR) spectra

were recorded on a Varian 1000 Scimitar Series or an ABB Bomem MB series spectrometer. Absorptions are given in wavenumbers ( $\text{cm}^{-1}$ ). High resolution mass spectrometry (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70 eV at the Ottawa-Carleton Mass Spectrometry Center or on a Bruker Maxis Impact Quadrupole-Time of Flight Mass Spectrometer in positive ESI mode at the McGill Chemistry Mass Spectrometry Center.

**1-((2-methylpent-4-en-2-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.79)**



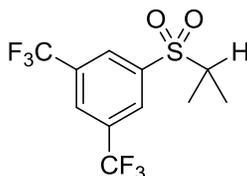
**$^1\text{H}$  NMR** ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.33 (s, 2H), 8.17 (s, 1H), 7.29 (ddt,  $J = 16.8, 10.0, 7.2$  Hz, 1H), 5.22 (d,  $J = 10.0$  Hz, 1H), 5.15 (d,  $J = 16.8$  Hz, 1H), 2.47 (d,  $J = 7.2$  Hz), 1.32 (s, 6H).

**$^{13}\text{C}$  NMR** ( $\text{CDCl}_3$ , 100 MHz):  $\delta$  138.6, 132.8 (q,  $J = 33$  Hz), 130.7 (d,  $J = 3$  Hz), 130.6, 127.3 (septet,  $J = 3$  Hz), 122.4 (q,  $J = 272$  Hz), 63.5, 39.2, 20.5.

**$^{19}\text{F}$  NMR** (376 MHz):  $\delta$  -63.8.

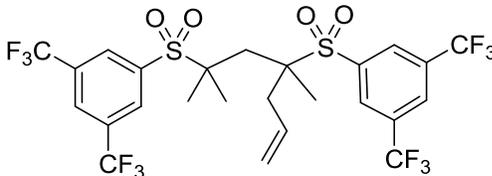
**HRMS**:  $m/z$  calcd for  $\text{C}_{14}\text{H}_{14}\text{F}_6\text{NaO}_2\text{S}$ : 383.0516; Found: 383.0505.

**1-(Isopropylsulfonyl)-3,5-bis(trifluoromethyl)benzene (3.105)**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.35 (s, 2H), 8.17 (s, 1H), 3.29 (septet, *J* = 6.8 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 6H).

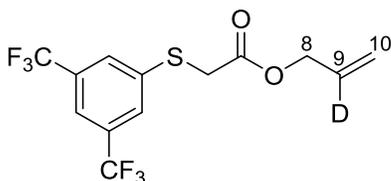
**5,5'-(2,4-dimethylhept-6-ene-2,4-diyl)disulfonylbis(1,3-bis(trifluoromethyl)benzene) (4.1)**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.34 (s, 2H), 8.30 (s, 2H), 8.22 (overlapping singlet, 1H), 8.21 (overlapping singlet, 1H), 5.67 – 5.78 (m, 1H), 5.20 (d, *J* = 10.4, additional unresolved fine coupling, 1H), 5.09 (dd, *J* = 16.8, 1.2 Hz, 1H), 2.64 (dd, *J* = 7.6, 14.8 Hz, 1H), 2.49 (d, *J* = 15.2 Hz, 1H), 2.38 (d, *J* = 15.2 Hz, 1H), 2.16 (dd, *J* = 14.8, 6.8 Hz, 1H), 1.67 (s, 3H), 1.65 (s, 3H), 1.46 (s, 3H)

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 138.8, 137.9, 133.1 (q, *J* = 35 Hz), 133.0 (q, *J* = 35 Hz), 131.0 (unresolved fine coupling), 130.8 (unresolved fine coupling), 130.1, 127.8 (unresolved fine coupling), 127.6 (unresolved fine coupling), 122.3 (q, *J* = 271 Hz), 122.2 (q, *J* = 271 Hz), 121.5, 67.3, 65.9, 60.4, 41.6, 36.9, 22.3, 22.1, 21.3, 21.0, 14.2.

**Allyl-2-*d* 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate**

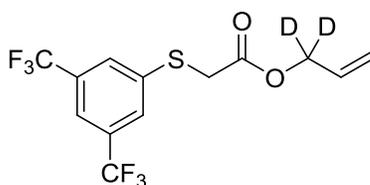


**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.81 (s, 2H), 7.70 (s, 1H), 5.28 – 5.31 (m, 1H), 5.25 – 5.26 (m, 1H), 4.63 (s, 2H), 4.63 (s, 2H), 3.76 (s, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.5, 139.1, 132.5 (q, *J* = 33 Hz), 131.0 (t, *J* = 24 Hz) (C8, upfield α-deuterium isotope shift (0.1 ppm)), 128.8, 128.5 (some fine splitting), 123.1 (q, *J* = 271 Hz), 119.3 (C10, upfield β-deuterium isotope shift (0.2 ppm)), 66.6, 35.7.

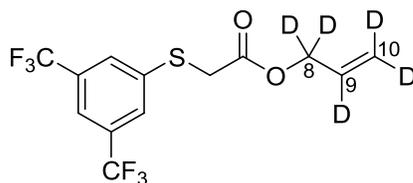
**<sup>19</sup>F NMR** (376 MHz): δ -64.1.

**Allyl-1,1-*d* 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate**



Sample was quite impure but after oxidation was purified successfully.

**Allyl-*d* 5 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate**



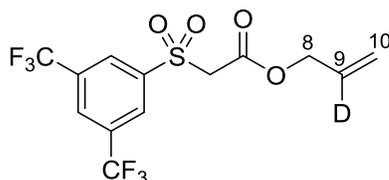
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.81 (s, 2H), 7.70 (s, 1H), 3.75 (s, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.5, 138.9, 132.4 (q, *J* = 33 Hz), 130.5 (t, *J* = 24 Hz) (C9, upfield α- (& β-) deuterium isotope shift (0.6 ppm)), 128.7 (d, *J* = 3 Hz), 123.0 (q, *J* = 272 Hz), 120.4 (septet, *J* = 4 Hz), 119.0 (quintet, *J* = 24 Hz) (C10, upfield α- (& β-) deuterium isotope shift (0.5 ppm)), 65.9 (quintet, *J* = 24 Hz) (C8, upfield α- (& β-)deuterium isotope shift (0.7 ppm)), 35.7.

**<sup>19</sup>F NMR** (376 MHz): δ -64.1.

**HRMS**: *m/z* calcd for C<sub>13</sub>H<sub>5</sub>D<sub>5</sub>F<sub>6</sub>KO<sub>2</sub>S: 388.0257; Found: 388.0467.

**Allyl-2-*d* 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate**

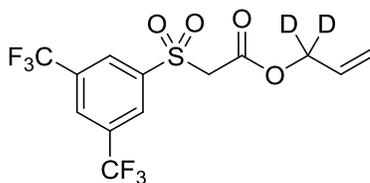


**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.41 (s, 2H), 8.18 (s, 1H), 5.31 (br s, 1H), 5.28 (s, 1H), 4.60 (s, 2H), 4.22 (s, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 161.6, 141.4, 133.2 (q, *J* = 35 Hz), 130.1 (t, *J* = 24 Hz) (C9, upfield α-deuterium isotope shift (0.2 ppm)), 129.5 (d, *J* = 3 Hz), 128.0 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 120.2 (C10, upfield β-deuterium isotope shift (0.2 ppm)), 67.3, 60.6.

**<sup>19</sup>F NMR** (376 MHz): δ - 63.9.

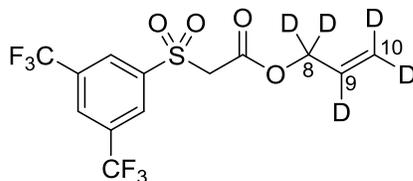
**Allyl-1,1-*d*2 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 7.81 (s, 2H), 7.70 (s, 1H), 5.86 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.31 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.2 Hz, 1H), 3.75 (s, 2H).

**HRMS:** *m/z* calcd for C<sub>13</sub>H<sub>8</sub>D<sub>2</sub>F<sub>6</sub>NaO<sub>4</sub>S: 401.0227; Found: 401.0222.

**Allyl-*d*<sub>5</sub> 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate**



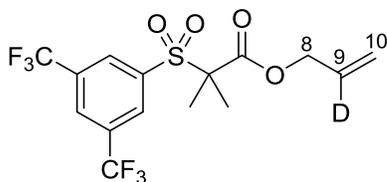
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.41 (s, 2H), 8.18 (s, 1H), 4.23 (s, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 161.7, 141.5, 133.2 (q, *J*<sup>2</sup><sub>C-F</sub> = 35 Hz), 130.0 (t, *J*<sup>1</sup><sub>C-D</sub> = 25 Hz) (C9, upfield α- (& β-) deuterium isotope shift (0.3 ppm)), 129.5 (d, *J*<sup>3</sup><sub>C-F</sub> = 4 Hz), 128.0 (septet, *J*<sup>3</sup><sub>C-F</sub> = 3 Hz), 122.5 (q, *J*<sup>1</sup><sub>C-F</sub> = 272 Hz), 119.8 (quintet, *J*<sup>1</sup><sub>C-D</sub> = 24 Hz) (C10, upfield α- (& β-) deuterium isotope shift (0.6 ppm)), 66.6 (quintet, *J*<sup>1</sup><sub>C-D</sub> = 23 Hz) (C8, upfield α- (& β-) deuterium isotope shift (0.7 ppm)), 60.6.

**<sup>19</sup>F NMR** (376 MHz): δ -63.9.

**HRMS:** *m/z* calcd for C<sub>13</sub>H<sub>5</sub>D<sub>5</sub>F<sub>6</sub>NaO<sub>4</sub>S: 404.0416; Found: 404.0403.

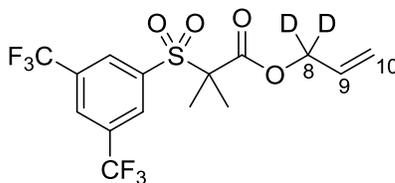
**Allyl-2-*d* 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-methylpropanoate**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.31 (s, 2H), 8.16 (s, 1H), 5.29 – 5.32 (m, 1H), 5.28 – 5.29 (m, 1H), 4.59 (s, 2H), 1.68 (s, 6H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.3 (minor product), 167.9, 138.9 (minor product), 138.8, 132.5 (q,  $J^2_{C-F} = 35$  Hz), 130.9 (d,  $J^3_{C-F} = 3$  Hz), 130.1 (t,  $J^1_{C-D} = 24$  Hz) (C9, upfield α-deuterium isotope shift (0.3 ppm)), 127.6 (septet,  $J^3_{C-F} = 3$  Hz), 122.4 (q,  $J^1_{C-F} = 272$  Hz), 119.6 (C10, upfield β-deuterium isotope shift (0.3 ppm)), 69.9, 69.8 (minor product), 68.1 (minor product), 67.0, 20.0, 9.8 (minor product).

**Allyl-1,1-*d*<sub>2</sub> 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-methylpropanoate**

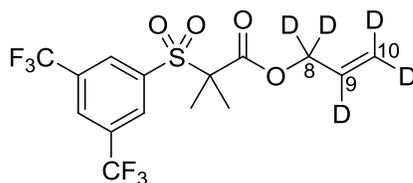


**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.30 (s, 2H), 8.16 (s, 1H), 5.83 (dd,  $J = 17.2, 10.4$  Hz, 1H), 5.32 (overlapping dd,  $J =$  large coupling constant unresolved, 1.2 Hz, 1H), 5.29 (overlapping dd,  $J =$  large coupling constant unresolved, 1.2 Hz, 1H), 1.68 (s, 6H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 167.9, 138.8, 132.5 (q,  $J^2_{C-F} = 34$  Hz), 130.9 (d,  $J^3_{C-F} = 4$  Hz), 130.3 (C9, upfield β-deuterium isotope shift (0.1 ppm)), 127.6 (septet,  $J^3_{C-F} = 3$  Hz), 122.4 (q,  $J^1_{C-F} = 272$  Hz), 119.9, 69.9, 66.5 (quintet,  $J^1_{C-D} = 23$  Hz) (C8, upfield α-deuterium isotope shift (0.4 ppm)), 20.0.

**HRMS:**  $m/z$  calcd for C<sub>15</sub>H<sub>12</sub>D<sub>2</sub>F<sub>6</sub>NaO<sub>4</sub>S: 429.0540; Found: 429.0529.

**Allyl-*d*<sub>5</sub> 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-methylpropanoate**



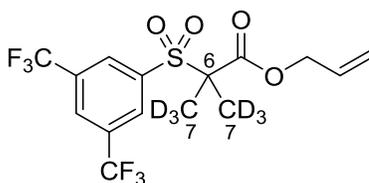
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.30 (s, 2H), 8.16 (s, 1H), 1.68 (s, 6H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 167.9, 138.8, 132.5 (q,  $J^2_{C-F}$  = 34 Hz), 130.9 (d,  $J^3_{C-F}$  = 3 Hz), 129.8 (t,  $J^1_{C-D}$  = 24 Hz) (C9, upfield α- (& β-) deuterium isotope shift (0.6 ppm)), 127.8 (septet,  $J^3_{C-F}$  = 3 Hz), 122.4 (q,  $J^1_{C-F}$  = 272 Hz), 119.3 (quintet,  $J^1_{C-D}$  = 24 Hz) (C10, upfield α- (& β-) deuterium isotope shift (0.6 ppm)), 69.9, 66.4 (quintet,  $J^1_{C-D}$  = 22 Hz) (C8, upfield α- (& β-) deuterium isotope shift (0.5 ppm)), 20.0.

**<sup>19</sup>F NMR** (376 MHz): δ – 63.8.

**HRMS**: m/z calcd for C<sub>15</sub>H<sub>9</sub>D<sub>5</sub>F<sub>6</sub>NaO<sub>4</sub>S: 432.0729; Found: 432.0718.

**Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-(methyl-*d*<sub>3</sub>)propanoate-3,3,3-*d*<sub>3</sub>**

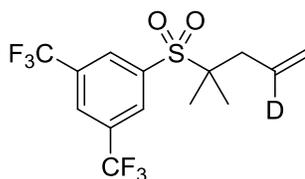


**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.32 (s, 2H), 8.18 (s, 1H), 5.86 (ddt,  $J$  = 17.1, 10.4, 5.6 Hz, 1H), 5.29 – 5.36 (overlapping dd, unresolved, 2H), 4.62 (ddd,  $J$  = 6.0, 2.0, 2.0 Hz, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 168.0, 138.7, 132.5 (q, *J* = 35 Hz), 130.9 (d, *J* = 3 Hz), 130.4, 127.6 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 119.8, 69.5 (C6, upfield β-deuterium isotope shift (0.4 ppm)), 67.1, 19.2 (unresolved splitting) (C7, upfield α-deuterium isotope shift (0.8 ppm)).

**HRMS:** *m/z* calcd for C<sub>15</sub>H<sub>8</sub>D<sub>6</sub>F<sub>6</sub>NaO<sub>4</sub>S: 433.0791; Found: 433.0771.

**1-((2-methylpent-4-en-2-yl-4-d)sulfonyl)-3,5-bis(trifluoromethyl)benzene**

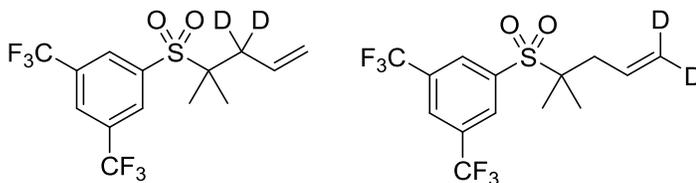


**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.33 (s, 2H), 8.17 (s, 1H), 5.22 (s, 1H), 5.15 (d, *J* = 1.2 Hz, 1H), 2.46 (s, 2H), 1.32 (s, 6H).

**1-((2-methylpent-4-en-2-yl-3,3-d2)sulfonyl)-3,5-bis(trifluoromethyl)benzene**

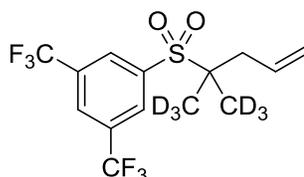
**& 1-((2-methylpent-4-en-2-yl-5,5-d2)sulfonyl)-3,5-**

**bis(trifluoromethyl)benzene**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.33 (s, 2H), 8.17 (s, 1H), 5.69 – 5.75 (m, 1H), 5.22 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.16 (dd, *J* = 16.8, 1.6 Hz, 1H), 3.46 (d, *J* = 7.2 Hz, 1H), 1.320 (overlapping s, 3H), 1.316 (overlapping s, 3H).

**1-((2-(methyl-*d*<sub>3</sub>)pent-4-en-2-yl-1,1,1-*d*<sub>3</sub>)sulfonyl)-3,5-bis(trifluoromethyl)benzene (4.39)**



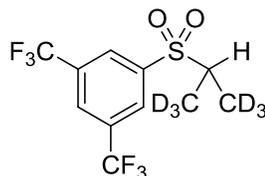
**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.33 (s, 2H), 8.17 (s, 1H), 5.73 (ddt, *J* = 17.6, 10.0, 7.6 Hz, 1H), 5.22 (dd, unresolved, 1H), 5.16 (dd, *J* = 16.8, 1.6 Hz, 1H), 2.45 (d, *J* = 7.6 Hz, 2H).

**<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz): δ 138.6, 132.8 (q, *J* = 35 Hz), 130.7 (d, *J* = 3 Hz), 130.6, 127.3 (septet, *J* = 3 Hz), 122.4 (q, *J* = 272 Hz), 120.8, 63.1, 39.1, 19.7 (septet, *J* = 20 Hz).

**<sup>19</sup>F NMR** (376 MHz): δ -63.8.

**HRMS**: *m/z* calcd for C<sub>14</sub>H<sub>8</sub>D<sub>6</sub>F<sub>6</sub>NaO<sub>2</sub>S: 389.0893; Found: 389.0892.

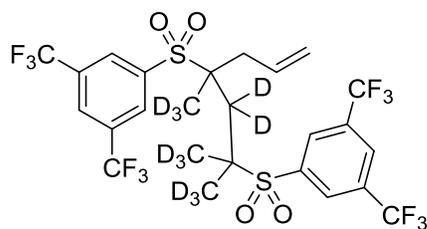
**1-((propan-2-yl-1,1,1,3,3,3-*d*<sub>6</sub>)sulfonyl)-3,5-bis(trifluoromethyl)benzene**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.35 (s, 2H), 8.17 (s, 1H), 3.25 (br s, 1H).

**HRMS**: *m/z* calcd for C<sub>11</sub>H<sub>4</sub>D<sub>6</sub>F<sub>6</sub>NaO<sub>2</sub>S: 349.0580; Found: 349.0571.

**5,5'-(2,4-bis(methyl-*d*<sub>3</sub>)hept-6-ene-2,4-diyl)disulfonyl-1,1,1,3,3-*d*<sub>5</sub>bis(1,3-bis(trifluoromethyl)benzene)**



**<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz): δ 8.35 (s, 2H), 8.32 (s, 2H), 8.19 (2 overlapping s, 2H), 5.65 – 5.73 (m, 1H), 5.18 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.07 (dd, *J* = 16.8, 1.6 Hz, 1H), 2.61 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.13 (dd, *J* = 14.4, 6.8 Hz, 1H).

## Chapter 5 : Publications & Conference Presentations

### Journal Articles:

1. Gill, Monica A.; Manthorpe, Jeffrey M. Mild, Rapid, and Inexpensive Microwave-Assisted Synthesis of Allylic and Propargylic Esters. *Synth. Commun.* **2013**, *43*, 1460-1468.
2. ‡Kong, Han Il; ‡Gill, Monica A.; Hrdina, Amy H.; Crichton, Jennifer E.; Manthorpe, Jeffrey M. Reactivity of  $\alpha$ -trifluoromethanesulfonyl esters, amides and ketones: Decarboxylative allylation, methylation, and enol formation. *J. Fluorine Chem.* **2013**, *153*, 151-161. (‡ These authors contributed equally)

### Book Chapter:

1. Manthorpe, J.M.; Kong, H.I.; Palko, J.W; Gill, M.A. Reduction of Sulfur-Carbon Bonds and of Other Heteroatoms Bonded to Tetrahedral Carbon. In: Gary A. Molander and Paul Knochel (eds.), *Comprehensive Organic Synthesis*, 2<sup>nd</sup> edition, Vol 8, Oxford: Elsevier; 2014, pp. 1031-1085.

### Oral Presentations:

1. Gill, M.\*, Manthorpe, J. Pd-Catalyzed Decarboxylative Allylation of Electron-Deficient Sulfones. Oral Presentation at the Quebec-Ontario Mini-Symposium on Biological and Organic Chemistry (QOMSBOC), Ryerson University, November 2014
2. Gill, M.\*, Manthorpe, J. Palladium Catalyzed Decarboxylative Allylation of Electron-Deficient Sulfones. Oral Presentation at OCCI Day, May 2014.
3. Gill, M.\*, Manthorpe, J. Mechanistic Insight into Palladium-Catalyzed Decarboxylative Allylation of Electron Deficient Sulfones. Oral Presentation at CSC 2011, Montreal, June 2011.

### Poster Presentations:

1. Gill, M.\*, Manthorpe, J. Pd-Catalyzed Decarboxylative Allylation of Sulfones: Reaction Development, Substrate Scope & Mechanistic Insight. Poster Presentation at 19<sup>th</sup> International Symposium on Homogeneous Catalysis (ISHC-XIX), Ottawa, Ontario, July 2014.

2. Gill, M.\*, Manthorpe, J. Mechanistic Insight Into Palladium Catalyzed Decarboxylative Allylation of Sulfones. Poster Presentation at IUPAC International Symposia on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 17), Fort Collins, Colorado, July 2013.
3. Gill, M.\*, Manthorpe, J. Mechanistic Investigation of Palladium Catalyzed Decarboxylative Allylation of Sulfones. Poster Presentation at Synthesis Day, University of Ottawa, May 2012.
4. Gill, M.\*, Manthorpe, J. Mechanistic Investigation of Palladium Catalyzed Decarboxylative Allylation of Sulfones. Poster Presentation at OCCI Day, May 2012.
5. Gill, M.\*, Hrdina, A.; Kong, H., Manthorpe, J. Decarboxylative Allylation Using Electron Deficient Sulfones. Poster Presentation at the Quebec-Ontario Mini-Symposium on Biological and Organic Chemistry (QOMSBOC), Brock University, November 2010.
6. Gill, M.\*, Hrdina, A.; Manthorpe, J. Decarboxylative Allylation of  $\alpha,\alpha$ -Dialkyl Trifluoromethyl Sulfones. Poster Presentation at Synthesis Day, University of Ottawa, June 2009.
7. Gill, M.\*, Hrdina, A.; Manthorpe, J. Decarboxylative Allylation of  $\alpha,\alpha$ -Dialkyl Trifluoromethyl Sulfones. Poster Presentation at CSC Conference, Hamilton, Ontario, May 2009.
8. Gill, M.\*; Hrdina, A.; Manthorpe, J. Decarboxylative Allylation of Triflones. Poster Presentation at the Quebec-Ontario Mini-Symposium on Biological and Organic Chemistry (QOMSBOC), University of Toronto, November 2008.

## Chapter 6 : References

- (1) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.
- (2) Rodríguez, N.; Goossen, L. J. Decarboxylative Coupling Reactions: A Modern Strategy for C–C-Bond Formation. *Chem. Soc. Rev.* **2011**, *40*, 5030–5048.
- (3) Tsuji, J.; Takahashi, H.; Morikawa, M. Organic Syntheses by Means of Noble Metal Compounds XVII. Reaction of  $\pi$ -Allylpalladium Chloride with Nucleophiles. *Tetrahedron Lett.* **1965**, *6*, 4387–4388.
- (4) Hata, G.; Takahashi, K.; Miyake, A. Palladium-Catalysed Exchange of Allylic Groups. *Chem. Commun.* **1970**, 1392–1393.
- (5) Atkins, K. E.; Walker, W. E.; Manyik, R. M. Palladium Catalyzed Transfer of Allylic Groups. *Tetrahedron Lett.* **1970**, *11*, 3821–3824.
- (6) Trost, B. M.; Strege, P. E. Asymmetric Induction in Catalytic Allylic Alkylation. *J. Am. Chem. Soc.* **1977**, *99*, 1649–1651.
- (7) Trost, B. M. New Rules of Selectivity: Allylic Alkylations Catalyzed by Palladium. *Acc. Chem. Res.* **1980**, *13*, 385–393.
- (8) Trost, B. M.; Van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395–422.
- (9) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. Facile Generation of a Reactive Palladium(II) Enolate Intermediate by the Decarboxylation of Palladium (II)  $\beta$ -Ketocarboxylate and Its Utilization in Allylic Acylation. *J. Am. Chem. Soc.* **1980**, *102*, 6381–6384.
- (10) Shimizu, I.; Yamada, T.; Tsuji, J. Palladium-Catalyzed Rearrangement of Allylic Esters of Acetoacetic Acid to Give  $\gamma,\delta$ -Unsaturated Methyl Ketones. *Tetrahedron Lett.* **1980**, *21*, 3199–3202.
- (11) Tsuji, J.; Minami, I.; Shimizu, I. Palladium-Catalyzed Allylation of Ketones and Aldehydes via Allyl Enol Carbonates. *Tetrahedron Lett.* **1983**, *24*, 1793–1796.
- (12) Burger, E. C.; Tunge, J. Asymmetric Allylic Alkylation of Ketone Enolates: An Asymmetric Claisen Surrogate. *Org. Lett.* **2004**, *6*, 4113–4115.

- (13) Burger, E. C.; Tunge, J. Transition Metal Catalyzed Decarboxylative Additions of Enolates. *Eur. J. Org. Chem.* **2005**, 1715–1726.
- (14) Behenna, D. C.; Stoltz, B. M. The Enantioselective Tsuji Allylation. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.
- (15) White, D.; Stewart, I.; Grubbs, R. H.; Stoltz, B. M. The Catalytic Asymmetric Total Synthesis of Elatol. *J. Am. Chem. Soc.* **2008**, *130*, 810–811.
- (16) White, D. E.; Stewart, I. C.; Seashore-Ludlow, B.; Grubbs, R. H.; Stoltz, B. M. A General Enantioselective Route to the Chamigrene Natural Product Family. *Tetrahedron* **2010**, *66*, 4668–4686.
- (17) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.  $\eta^2$ -dba Complexes of Pd(0): The Substituent Effect in Suzuki-Miyaura Coupling. *Org. Lett.* **2004**, *6*, 4435–4438.
- (18) Enquist, Jr, J. A.; Stoltz, B. M. The Total Synthesis of (-)-Cyanthiwigin F by Means of Double Catalytic Enantioselective Alkylation. *Nature* **2008**, *453*, 1228–1231.
- (19) Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. Transition Metal-Catalyzed Decarboxylative Allylation and Benzylolation Reactions. *Chem. Rev.* **2011**, *111*, 1846–1913.
- (20) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. Unusual Allylpalladium Carboxylate Complexes: Identification of the Resting State of Catalytic Enantioselective Decarboxylative Allylic Alkylation Reactions of Ketones. *Angew. Chem. Int. Ed.* **2009**, *48*, 6840–6843.
- (21) Keith, J.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. The Inner-Sphere Process in the Enantioselective Tsuji Allylation Reaction with (S)-*t*-Bu-Phosphinooxazoline Ligands. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.
- (22) Keith, J.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. The Reaction Mechanism of the Enantioselective Tsuji Allylation: Inner-Sphere and Outer-Sphere Pathways, Internal Rearrangements, and Asymmetric C-C Bond Formation. *J. Am. Chem. Soc.* **2012**, *134*, 19050–19060.
- (23) Fiaud, J. C.; Aribi-Zouiouche, L. Stereochemistry in the Palladium-Catalyzed Rearrangement of Some Cyclohex-2-Enyl Acetoacetates. *Tetrahedron Lett.* **1982**, *23*, 5279–5282.

- (24) Chattopadhyay, K.; Jana, R.; Day, V. W.; Douglas, J. T.; Tunge, J. Mechanistic Origin of the Stereodivergence in Decarboxylative Allylation. *Org. Lett.* **2010**, *12*, 3042–3045.
- (25) Grenning, A. J.; Tunge, J. Rapid Decarboxylative Allylation of Nitroalkanes. *Org. Lett.* **2010**, *12*, 740–742.
- (26) Waetzig, S. R.; Tunge, J. Palladium-Catalyzed Decarboxylative  $sp^3$ - $sp^3$  Coupling of Nitrobenzene Acetic Esters. *J. Am. Chem. Soc.* **2007**, *129*, 14860–14861.
- (27) Recio III, A.; Tunge, J. Regiospecific Decarboxylative Allylation of Nitriles. *Org. Lett.* **2009**, *11*, 5630–5633.
- (28) Hrdina, A. H. I. Preliminary Investigation of a Catalytic Tsuji-Trost Reaction of  $\beta$ -Sulfonyl Esters, BSc Thesis, Carleton University, 2008.
- (29) Sheppard, W. The Effect of Fluorine Substitution on the Electronic Properties of Alkoxy, Alkylthio and Alkylsulfonyl Groups. *J. Am. Chem. Soc.* **1963**, *85*, 1314–1318.
- (30) Eugene, F.; Langlois, B.; Laurant, E. Improved Synthesis for the Preparation of Trifluoromethyl Sulfones Used as Intermediates of Di- or Tri-Substituted Olefins. *J. Fluor. Chem.* **1994**, *66*, 301–309.
- (31) Shimizu, I.; Tsuji, J. Palladium-Catalyzed Decarboxylation-Dehydrogenation of Allyl  $\beta$ -Keto Carboxylates and Allyl Enol Carbonates as a Novel Synthetic Method for  $\alpha$ -Substituted  $\alpha,\beta$ -Unsaturated Ketones. *J. Am. Chem. Soc.* **1982**, *104*, 5844–5846.
- (32) Trost, B. M.; Xu, J. Regio- and Enantioselective Pd-Catalyzed Allylic Alkylation of Ketones through Allyl Enol Carbonates. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847.
- (33) Goumont, R.; Magnier, E.; Kizilian, E.; Terrier, F. Acidity Inversions of  $\alpha$ -NO<sub>2</sub> and  $\alpha$ -SO<sub>2</sub>CF<sub>3</sub> Activated Carbon Acids as a Result of Contrasting Solvent Effects on Transfer from Water to Dimethyl Sulfoxide Solutions. *J. Org. Chem.* **2003**, *68*, 6566–6570.
- (34) Kolthoff, I. M.; Chantooni, M. K.; Bhowmik, S. Dissociation Constants of Uncharged and Monovalent Cation Acids in Dimethyl Sulfoxide. *J. Am. Chem. Soc.* **1967**, *90*, 23–28.
- (35) Bordwell, F. G.; Algrim, D. Nitrogen Acids. 1. Carboxamides and Sulfonamides. *J. Org. Chem.* **1976**, *41*, 2507–2508.

- (36) Hendrickson, J. B.; Bair, K. W. New Methods for the Synthesis of Triflones. *J. Org. Chem.* **1977**, *42*, 3875–3878.
- (37) Hendrickson, J. B.; Bair, K. W.; Bergeron, R.; Giga, A.; Skipper, P. L.; Sternbach, D. D.; Wareing, J. Uses of the Triflyl Group in Organic Synthesis. *Org. Prep. Proced. Int.* **1977**, *9*, 173–207.
- (38) Freeman, P. K.; Larry, L. Organolithium Reagents From Alkyl Halides and Lithium Di-*tert*-Butylbiphenyl. *Tetrahedron* **1976**, *22*, 1849–1852.
- (39) Freeman, P. K. Alkylolithium Reagents from Alkyl Halides and Lithium Radical Anions. *J. Org. Chem.* **1980**, *301*, 1924–1930.
- (40) Comins, D. L.; Dehghani, A. Pyridine-Derived Triflating Reagents: An Improved Preparation of Vinyl Triflates from Metallo Enolates. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.
- (41) Creary, X. Reaction of Triflic Anhydride with Grignard Reagents. Oxidizing Properties of Triflic Anhydride. *J. Org. Chem.* **1980**, *45*, 2727–2729.
- (42) Andersen, K. K. Synthesis of (+)-Ethyl *p*-Tolyl Sulfoxide from (-)-Menthyl (-)-*p*-Toluenesulfinate. *Tetrahedron Lett.* **1962**, *3*, 93–95.
- (43) Fernandez, I.; Khiar, N.; Llera, J. M.; Alcudia, F. Asymmetric Synthesis of Alkane- and Arenesulfonates of Diacetone-D-Glucose (DAG): An Improved and General Route to Both Enantiomerically Pure Sulfoxides. *J. Org. Chem.* **1992**, *57*, 6789–6796.
- (44) Hendrickson, J. B.; Skipper, P. L. Synthetic Manipulation of the Triflone Group. *Tetrahedron* **1976**, *32*, 1627–1635.
- (45) Jablonski, L.; Joubert, J.; Billard, T.; Langlois, B. Trifluoroacetic Acid Derivatives as Nucleophilic Trifluoromethylating. *Synlett* **2002**, 230–232.
- (46) Inschauspe, D.; Sortais, J.-B.; Billard, T.; Langlois, B. Trifluoromethanesulfinic Acid Derivatives as Nucleophilic Trifluoro-Methylating Reagents. *Synlett* **2003**, 233–235.
- (47) Ruppert, I.; Schlich, K.; Volbach, W. Die Ersten CF<sub>3</sub>-Substituierten Organyl(Chlor)Silane. *Tetrahedron Lett.* **1984**, *25*, 2195–2198.
- (48) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. Fluoride-Induced Trifluoromethylation of Carbonyl Compounds with

Trifluoromethyltrimethylsilan (TMS-CF<sub>3</sub>). A Trifluoromethide Equivalent. *J. Am. Chem. Soc.* **1989**, *111*, 393–395.

- (49) Billard, T.; Large, S.; Langlois, B. Preparation of Trifluoromethyl Sulfides or Selenides from Trifluoromethyl Trimethylsilane and Thiocyanates or Selenocyanates. *Tetrahedron Lett.* **1997**, *38*, 65–68.
- (50) Granger, C.; Felix, C.; Parrot-Lopex, H.; Langlois, B. Fluorine Containing  $\beta$ -Cyclodextrin : A New Class of Amphiphilic Carriers. *Tetrahedron Lett.* **2000**, *41*, 9257–9260.
- (51) Billard, T.; Langlois, B. A New Simple Access to Trifluoromethyl Thioethers or Selenoethers from Trifluoromethyl Trimethylsilane and Disulfides or Diselenides. *Tetrahedron Lett.* **1996**, *37*, 6865–6868.
- (52) Behr, J.-B.; Chavaria, D.; Plantier-Royon, R. Trifluoromethide as a Strong Base: [CF<sub>3</sub><sup>-</sup>] Mediates Dichloromethylation of Nitrones by Proton Abstraction from the Solvent. *J. Org. Chem.* **2013**, *78*, 11477–11482.
- (53) Hendrickson, J. B.; Giga, A.; Wareing, J. Triflones (CF<sub>3</sub>SO<sub>2</sub>C). Survey of Reactivity and Synthetic Utility. *J. Am. Chem. Soc.* **1974**, *96*, 2275–2276.
- (54) Mander, L. N.; Sethi, S. P. Regioselective Synthesis of  $\beta$ -Ketoesters from Lithium Enolates and Methyl Cyanoformate. *Tetrahedron Lett.* **1983**, 5425–5428.
- (55) Donnelly, D.; Finet, J.-P.; Rattigan, B. A. Organolead-Mediated Arylation of Allyl  $\beta$ -Ketoesters: A Selective Synthesis of Isoflavanones and Isoflavones. *J. Chem Soc., Perkin Trans. 1* **1993**, 1729–1735.
- (56) Trost, B. M.; Xu, J. Enolates by Allyl 1*H*-Imidazole-1-Carboxylate Mediated with Boron Trifluoride Etherate. A Convenient Procedure for the Synthesis of Substituted Allyl Enol Carbonates. *J. Org. Chem.* **2007**, *72*, 9372–9375.
- (57) Terrier, F.; Kizilian, E.; Goumont, R.; Faucher, N.; Wakselman, C.  $\alpha$ -Sulfonyl Carbanions: Combined Kinetic, Thermodynamic, and NMR Approaches for the Study of the Ionization of Benzyltriflones in Me<sub>2</sub>SO and H<sub>2</sub>O–Me<sub>2</sub>SO Mixtures. *J. Am. Chem. Soc.* **1998**, *120*, 9496–9503.
- (58) Berger, S. T.; Ofial, A. R.; Mayr, H. Inverse Solvent Effects in Carbocation Carbanion Combination Reactions: The Unique Behavior of Trifluoromethylsulfonyl Stabilized Carbanions. *J. Am. Chem. Soc.* **2007**, *129*, 9753–9761.

- (59) Goumont, R.; Kizilian, E.; Buncel, E.; Terrier, F. Super Acidifiers: The Origin of the Exceptional Electron Transmission Capability of the SO<sub>2</sub>CF<sub>3</sub> Group in Carbanion Stabilization. *Org. Biomol. Chem.* **2003**, *1*, 1741–1748.
- (60) Hellmann, G.; Hack, A.; Thiemermann, E.; Luche, O.; Raabe, G.; Gais, H.-J. Chiral Fluorinated  $\alpha$ -Sulfonyl Carbanions: Enantioselective Synthesis and Electrophilic Capture, Racemization Dynamics, and Structure. *Chem. Eur. J.* **2013**, *19*, 3869–3897.
- (61) Gais, H.-J.; Hellmann, G.; Giinther, H.; Lopez, F.; Lindner, H. J.; Braun, S. Are Lithiosulfones Configurationally Stable? *Angew. Chem. Int. Ed.* **1989**, *28*, 1025–1028.
- (62) Gais, H.-J.; Hellmann, G. Stereochemistry of Chiral, Nonracemic Lithium Salts of Acyclic  $\alpha$ -Sulfonyl Carbanions: The Asymmetric Induction Exerted by the Lithium-Coordinated Sulfonyl Group. *J. Am. Chem. Soc.* **1992**, *114*, 4439–4440.
- (63) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. Picolinoxy Group, a New Leaving Group for Anti SN2' Selective Allylic Substitution with Aryl Anions Based on Grignard Reagents. *Org. Lett.* **2008**, *10*, 1719–1722.
- (64) Kong, H. II. Regioselective Methylation of  $\alpha$ -Trifluoromethanesulfonyl Carbonyl Compounds and Iridium Catalyzed Decarboxylative Allylation of Allyl 3,5-Bis (trifluoromethylphenyl) Sulfonylacetate, MSc Thesis, Carleton University, 2011.
- (65) Lebar, M. D.; Baker, B. J. Synthesis of the C3-14 Fragment of Palmerolide A Using a Chiral Pool Based Strategy. *Tetrahedron* **2010**, *66*, 1557–1562.
- (66) Ogawa, K.; Ohta, S.; Okamoto, M. Reaction of Terminal Oxiranes With Arenesulfonic Acid. *Synthesis* **1987**, 281–284.
- (67) Weaver, J. D.; Tunge, J. Decarboxylative Allylation Using Sulfones as Surrogates of Alkanes. *Org. Lett.* **2008**, *10*, 4657–4660.
- (68) Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.
- (69) Alonso, D.; Nájera, C.; Varea, M.  $\pi$ -Deficient  $\alpha$ -Arylsulfonyl Esters as Soft Nucleophiles in Organic Synthesis. *Tetrahedron Lett.* **2001**, *42*, 8845–8848.

- (70) Alonso, D.; Nájera, C.; Varea, M. Synthesis and Reactivity of  $\pi$ -Electron-Deficient (Arylsulfonyl)acetates. *Helv. Chim. Acta.* **2002**, *85*, 4287–4305.
- (71) Newman, M. S.; Karnes, H. A. The Conversion of Phenols to Thiophenols via Dialkylthiocarbamates. *J. Org. Chem.* **1966**, *31*, 3980–3984.
- (72) Evans, E. R.; Kwart, H. The Vapor Phase Rearrangement of Thioncarbonates and Thioncarbarnates. *J. Org. Chem.* **1966**, *31*, 410–413.
- (73) Lloyd-Jones, G.; Moseley, J.; Renny, J. Mechanism and Application of the Newman-Kwart O→S Rearrangement of O-Aryl Thiocarbarnates. *Synthesis* **2008**, 661–689.
- (74) Burns, M.; Lloyd-Jones, G. C.; Moseley, J. D.; Renny, J. S. The Molecularity of the Newman-Kwart Rearrangement. *J. Org. Chem.* **2010**, *75*, 6347–6353.
- (75) Samreth, S.; Bellamy, F.; Bajgrowicz, J.; Barverousse, V.; Renaut, P. Nouveaux Beta-D-Phenyl-Thioxylosides, Leur Procédé de Préparation et Leur Utilisation En Thérapeutique, EP 0 365 397 A2, 1990.
- (76) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. Titanate-Mediated Transesterifications with Functionalized Substrates. *Synthesis* **1982**, *1982*, 138–141.
- (77) Kondaiah, G. C. M.; Reddy, L. A.; Babu, K. S.; Gurav, V. M.; Hüge, K. G.; Bandichhor, R.; Reddy, P. P.; Bhattacharya, A.; Anand, R. V. Boric Acid: An Efficient and Environmentally Benign Catalyst for Transesterification of Ethyl Acetoacetate. *Tetrahedron Lett.* **2008**, *49*, 106–109.
- (78) Neises, B.; Steglich, W. Simple Method for the Esterification of Carboxylic Acids. *Angew. Chem. Int. Ed.* **1978**, *17*, 522–524.
- (79) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. A Convenient Method for the Synthesis of Carboxylic Esters. *Chem. Lett.* **1975**, 1045–1048.
- (80) Mukaiyama, T. New Synthetic Reactions Based on the Onium Salts of Aza-Arenes. *Angew. Chem. Int. Ed.* **1979**, *18*, 707–721.
- (81) Gill, M.; Manthorpe, J. M. Mild, Rapid, and Inexpensive Microwave-Assisted Synthesis of Allylic and Propargylic Esters. *Synth. Commun.* **2013**, *43*, 1460–1468.

- (82) Nehru, K.; Kim, S. S.; Kim, D. W.; Jung, H. C. A Mild and Highly Efficient Oxidation of Sulfides to Sulfoxides with Periodic Acid Catalyzed by FeCl<sub>3</sub>. *Synthesis* **2002**, 2484–2486.
- (83) Alonso, D. A.; Najera, C.; Varea, M. Simple, Economical and Environmentally Friendly Sulfone Synthesis. *Tetrahedron Lett.* **2002**, *43*, 3459–3461.
- (84) Jeyakumar, K.; Chakravarthy, R. D.; Chand, D. K. Simple and Efficient Method for the Oxidation of Sulfides to Sulfones Using Hydrogen Peroxide and a Mo(VI) Based Catalyst. *Catal. Commun.* **2009**, *10*, 1948–1951.
- (85) Evans, D.; Kværnø, L.; Dunn, T. B.; Beauchemin, A.; Raymer, B.; Mulder, J.; Olhava, E. J.; Juhl, M.; Kagechika, K.; Favor, D. Total Synthesis of (+)-Azaspiracid-1. An Exhibition of the Intricacies of Complex Molecule Synthesis. *J. Am. Chem. Soc.* **2008**, *130*, 16295–16309.
- (86) Wilde, A.; Otte, A. R.; Hoffmann, H. M. R. Cyclopropanes via Nucleophilic Attack at the Central Carbon of ( $\pi$ -Allyl)palladium Complexes. *Chem. Commun.* **1993**, 615–616.
- (87) Otte, A. R.; Wilde, A.; Hoffmann, H. M. R. Cyclopropanes by Nucleophilic Attack of Mono- and Diaryl-Substituted ( $\eta^3$ -Allyl)palladium Complexes: Aryl Effect and Stereochemistry. *Angew. Chem. Int. Ed.* **1994**, 1280–1282.
- (88) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. Isolation and X-Ray Crystal Structure of a Palladacyclobutane: Insight into the Mechanism of Cyclopropanation. *Angew. Chem. Int. Ed.* **1995**, *34*, 100–102.
- (89) Satake, A.; Nakata, T. Novel  $\eta^3$ -Allylpalladium-Pyridinylpyrazole Complex: Synthesis, Reactivity, and Catalytic Activity for Cyclopropanation of Ketene Silyl Acetal with Allylic Acetates. *J. Am. Chem. Soc.* **1998**, *120*, 10391–10396.
- (90) Satake, A.; Kadohama, H.; Koshino, H.; Nakata, T. Asymmetric Cyclopropanation of Ketene Silyl Acetal with Allylic Acetate Catalyzed by a Palladium Complex. *Tetrahedron Lett.* **1999**, *40*, 3597–3600.
- (91) Liu, W.; Chen, D.; Zhu, X. Z.; Wan, X. L.; Hou, X. L. Highly Diastereo- and Enantioselective Pd-Catalyzed Cyclopropanation of Acyclic Amides with Substituted Allyl Carbonates. *J. Am. Chem. Soc.* **2009**, *131*, 8734–8735.

- (92) Amatore, C.; Jutand, A. Role of dba in the Reactivity of palladium(0) Complexes Generated in Situ from Mixtures of Pd(dba)<sub>2</sub> and Phosphines. *Coord. Chem. Rev.* **1998**, *178–180*, 511–528.
- (93) Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M.; Mottier, L. Rates and Mechanisms of Oxidative Addition to Zerovalent Palladium Complexes Generated in Situ from Mixtures of Pd(0)(dba)<sub>2</sub> and Triphenylphosphine. *Organometallics* **1993**, *12*, 3168–3178.
- (94) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. Identification of the Effective Palladium(0) Catalytic Species Generated in Situ from Mixtures of Pd(dba)<sub>2</sub> and Bidentate Phosphine Ligands. Determination of Their Rates and Mechanism in Oxidative Addition. *J. Am. Chem. Soc.* **1997**, *119*, 5176–5185.
- (95) Fairlamb, I. J. S.  $\pi$ -Acidic Alkene Ligand Effects in Pd-Catalysed Cross-Coupling Processes: Exploiting the Interaction of Dibenzylidene Acetone (dba) and Related Ligands with Pd(0) and Pd(II). *Org. Biomol. Chem.* **2008**, *6*, 3645–3656.
- (96) Zalesskiy, S. S.; Ananikov, V. P. Pd<sub>2</sub>(dba)<sub>3</sub> as a Precursor of Soluble Metal Complexes and Nanoparticles : Determination of Palladium Active Species for Catalysis and Synthesis. *Organometallics* **2012**, *31*, 2302.
- (97) Ananikov, V. P.; Beletskaya, I. P. Toward the Ideal Catalyst: From Atomic Centers to a “Cocktail” of Catalysts. *Organometallics* **2012**, *31*, 1595–1604.
- (98) Kashin, A. S.; Ananikov, V. P. Catalytic C-C and C-Heteroatom Bond Formation Reactions: In Situ Generated or Preformed Catalysts? Complicated Mechanistic Picture behind Well-Known Experimental Procedures. *J. Org. Chem.* **2013**, *78*, 11117–11125.
- (99) Norton, D. M.; Mitchell, E.; Botros, N. R.; Jessop, P. G.; Baird, M. C. A Superior Precursor for Palladium(0)-Based Cross-Coupling and Other Catalytic Reactions. *J. Org. Chem.* **2009**, *74*, 6674–6680.
- (100) Fraser, A. W.; Besaw, J. E.; Hull, L. E.; Baird, M. C. Pd( $\eta^3$ -1-PhC<sub>3</sub>H<sub>4</sub>)( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>), an Unusually Effective Catalyst Precursor for Suzuki-Miyaura Cross-Coupling Reactions Catalyzed by Bis-Phosphine Palladium (0) Compounds. *Organometallics* **2012**, *31*, 2470–2475.
- (101) Jaksic, B. E.; Jiang, J.; Fraser, A. W.; Baird, M. C.  $\eta^5$ -Cyclopentadienyl- $\eta^3$ -1-Phenylallylpalladium, an Unusually Effective Catalyst Precursor for Copper-Free and Copper-Assisted Sonogashira Cross-Coupling Reactions Catalyzed by Bis-Phosphine Palladium(0) Compounds: The Role of Bis-

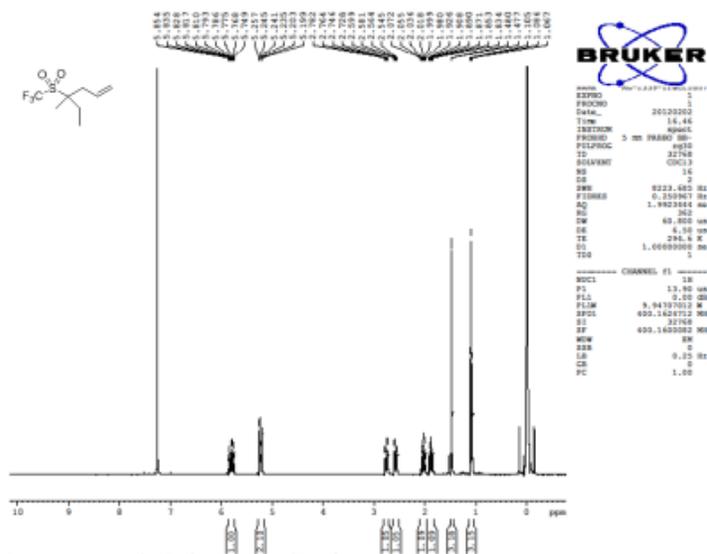
Acetylide Intermediates in the Reduction of a Palladium(II) Catalyst Precursor to a Palladium(0) Catalyst. *Organometallics* **2013**, *32*, 4192–4198.

- (102) Fraser, A. W.; Jaksic, B. E.; Batcup, R.; Sarsons, C. D.; Woolman, M.; Baird, M. C. Pd( $\eta^3$ -1-PhC<sub>3</sub>H<sub>4</sub>)( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>), an Unusually Effective Catalyst Precursor for Heck-Mizoroki and Sonogashira Cross-Coupling Reactions Catalyzed by Bis-Phosphine Palladium(0) Compounds. *Organometallics* **2013**, *32*, 9–11.
- (103) Borjian, S.; Tom, D. M. E.; Baird, M. C. Pd( $\eta^3$ -1-PhC<sub>3</sub>H<sub>4</sub>)( $\eta^5$ -C<sub>5</sub>H<sub>5</sub>) as a Catalyst Precursor for Buchwald-Hartwig Amination Reactions. *Organometallics* **2014**, *33*, 3928–3935.
- (104) Salomé, C.; Kohn, H. Triphenylphosphine Dibromide: A Simple One-Pot Esterification Reagent. *Tetrahedron* **2009**, *65*, 456–460.
- (105) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. Diverse Alkanones by Catalytic Carbon Insertion into the Formyl C-H Bond. Concise Access to the Natural Precursor of Achyrofuran. *Org. Lett.* **2009**, *11*, 3202–3205.
- (106) Chakraborti, A. K.; Singh, B.; Chankeshwara, S. V.; Patel, A. R. Protic Acid Immobilized on Solid Support as an Extremely Efficient Recyclable Catalyst System for a Direct and Atom Economical Esterification of Carboxylic Acids with Alcohols. *J. Org. Chem.* **2009**, *74*, 5967–5974.
- (107) Tsuji, J.; Nisar, M.; Shimizu, I. Facile Palladium-Catalyzed Decarboxylation Reaction of Allylic  $\beta$ -Keto Esters. *J. Org. Chem.* **1985**, *50*, 3416–3417.
- (108) Mandai, T.; Imaji, M.; Takada, H.; Kawata, M.; Nokami, J.; Tsuji, J. Facile Transformation of Substituted Allyl Malonates to Monocarboxylic Acids and Esters by the Reaction with Ammonium Formate Catalyzed by Palladium Complexes. *J. Org. Chem.* **1989**, *54*, 5395–5397.
- (109) Henin, F.; Muzart, J. Palladium-Catalyzed Cleavage of Prochiral Enol Carbonates: Enantioselective Ketonisation of Resulting Enols. *Tetrahedron: Asymmetry* **1992**, *3*, 1161–1164.
- (110) Aboulhoda, S.; Henin, F.; Muzart, J.; Thorey, C.; Behnen, W.; Martens, J.; Mehler, T. Production of Optically Active Ketones by a Palladium-Induced Cascade Reaction from Racemic  $\beta$ -Ketoesters. *Tetrahedron: Asymmetry* **1994**, *5*, 1321–1326.

- (111) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. Catalytic Enantioselective Decarboxylative Protonation. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349.
- (112) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. Homogeneous Pd-Catalyzed Enantioselective Decarboxylative Protonation. *Org. Lett.* **2008**, *10*, 1039–1042.
- (113) Johansson, R.; Wendt, O. F. Insertion of CO<sub>2</sub> into a Palladium Allyl Bond and a Pd(II) Catalysed Carboxylation of Allyl Stannanes. *Dalt. Trans.* **2007**, 488–492.
- (114) Li, X.; Li, C.; Zhang, W.; Lu, X.; Han, S.; Hong, R. Highly Stereoselective 7-*Endo-Trig*/ring Contraction Cascade to Construct Pyrrolo[1,2-*a*]quinoline Derivatives. *Org. Lett.* **2010**, *12*, 1696–1699.
- (115) Tsang, D. S.; Yang, S.; Alphonse, F.-A.; Yudin, A. K. Stereoselective Isomerisation of N-Allyl Aziridines into Geometrically Stable Z Enamines by Using Rhodium Hydride Catalysis. *Chem. Eur. J.* **2008**, *14*, 886–894.
- (116) Yamamoto, Y.; Al-Masum, M.; Asao, N. Palladium-Catalyzed Addition of Activated Methylene and Methyne Compounds to Allenes. *J. Am. Chem. Soc.* **1994**, *116*, 6019–6020.
- (117) Yamamoto, Y.; Fujiwara, N.; Asao, N. Remarkable Reversal of the Regioselectivity in the Palladium Catalyzed Hydrocarbon Reaction of Allenes with Methylmalonotrile. *Tetrahedron Lett.* **1995**, *36*, 2811–2814.
- (118) Yamamoto, Y. Palladium Catalyzed Hydrocarbonation of Olefins. *Pure Appl. Chem.* **1996**, *68*, 9–14.
- (119) Johansson, R.; Jarenmark, M.; Wendt, O. F. Insertion of Carbon Dioxide into (PCP)Pd(II) - Me Bonds. *Organometallics* **2005**, *24*, 4500–4502.
- (120) Wu, J.; Green, J. C.; Hazari, N.; Hruszkewycz, D. P.; Incarvito, C. D.; Schmeier, T. J. The Reaction of Carbon Dioxide with Palladium Allyl Bonds. *Organometallics* **2010**, *29*, 6369–6376.
- (121) Hruszkewycz, D. P.; Wu, J.; Hazari, N.; Incarvito, C. D. Palladium(I)-Bridging Allyl Dimers for the Catalytic Functionalization of CO<sub>2</sub>. *J. Am. Chem. Soc.* **2011**, *133*, 3280–3283.
- (122) Chatt, J.; Davidson, J. The Tautomerism of Arene and Ditertiary Phosphine Complexes of Ruthenium(0), and the Preparation of New Types of Hydrido-Complexes of Ruthenium(II). *J. Chem. Soc.* **1965**, 843–855.

- (123) Mohr, F.; Privér, S. H.; Bhargava, S. K.; Bennett, M. Ortho-Metallated Transition Metal Complexes Derived from Tertiary Phosphine and Arsine Ligands. *Coord. Chem. Rev.* **2006**, *250*, 1851–1888.
- (124) Clark, H. C.; Hine, K. E. Thermally Induced Ortho-Metalation of Dicarbomethoxy-Acetylenebis(triphenylphosphine)platinum. *J. Organometal. Chem.* **1976**, *105*, C32–C34.
- (125) Rice, N. C.; Oliver, J. D. The Crystal Structure of *o*-(diphenylphosphino)phenyl-*cis*-1,2-Dicarbomethoxyethyltriphenylphosphineplatinum. *J. Organometal. Chem.* **1978**, *145*, 121–138.
- (126) Tromp, M.; Sietsma, J. R.; van Bokhoven, J.; van Strijdonck, G. P. F.; van Haaren, R. J.; van der Eerden, A. M. J.; van Leeuwen, P. W. N. M.; Koningsberger, D. C. Deactivation Processes of Homogeneous Pd Catalysts Using in Situ Time Resolved Spectroscopic Techniques. *Chem. Commun.* **2003**, 128–129.
- (127) Markert, C.; Neuburger, M.; Kulicke, K.; Meuwly, M.; Pfaltz, A. Palladium-Catalyzed Allylic Substitution: Reversible Formation of Allyl-Bridged Dinuclear Palladium(I) Complexes. *Angew. Chem. Int. Ed.* **2007**, *46*, 5892–5895.
- (128) Powers, D. C.; Ritter, T. Bimetallic Pd(III) Complexes in Palladium-Catalysed Carbon–heteroatom Bond Formation. *Nat. Chem.* **2009**, *1*, 302–309.
- (129) Herrmann, W.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. Palladacycles as Structurally Defined Catalysts for the Heck Olefination of Chloro- and Bromoarenes. *Angew. Chem. Int. Ed.* **1995**, *34*, 1844–1848.









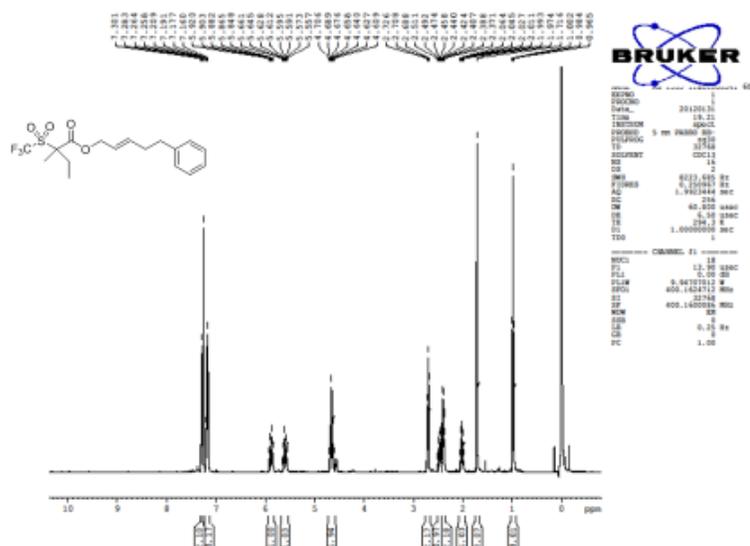


Figure A9: <sup>1</sup>H NMR for 5-Phenylpent-2-en-1-yl 2-methyl-2-((triflyl)butanoate (2.55)

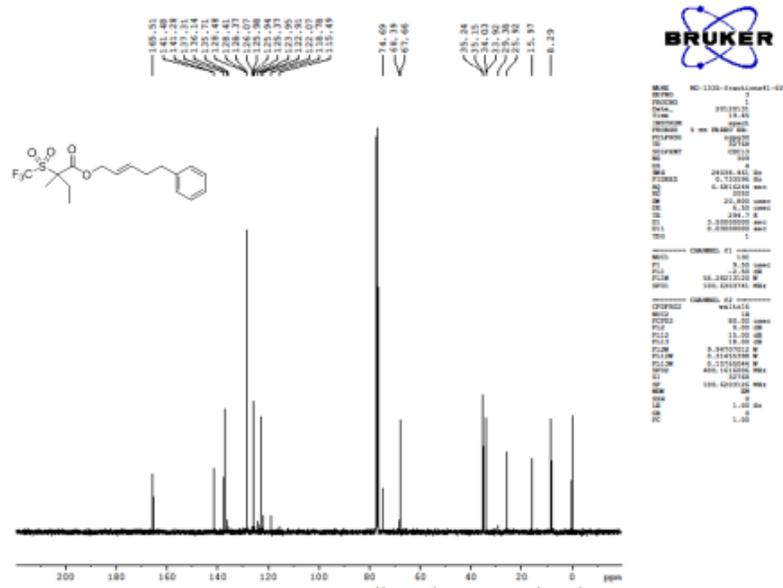


Figure A10: <sup>13</sup>C NMR for 5-Phenylpent-2-en-1-yl 2-methyl-2-((triflyl)butanoate (2.55)

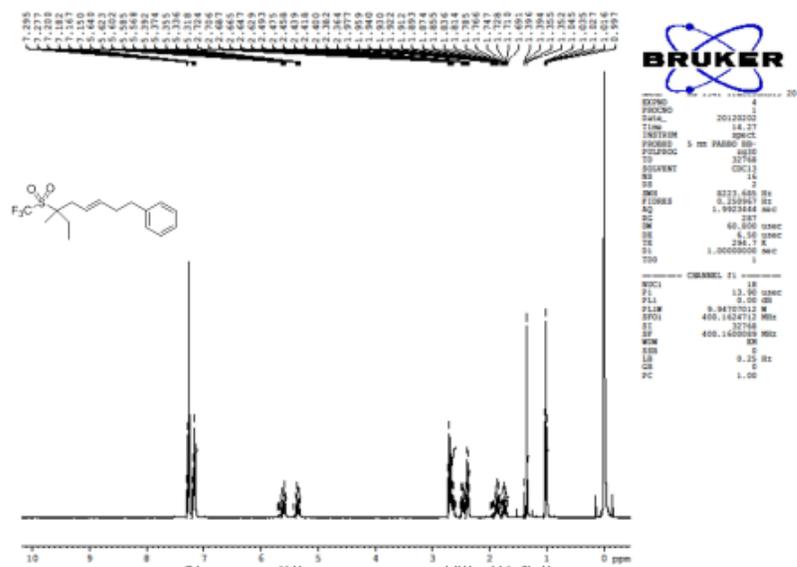
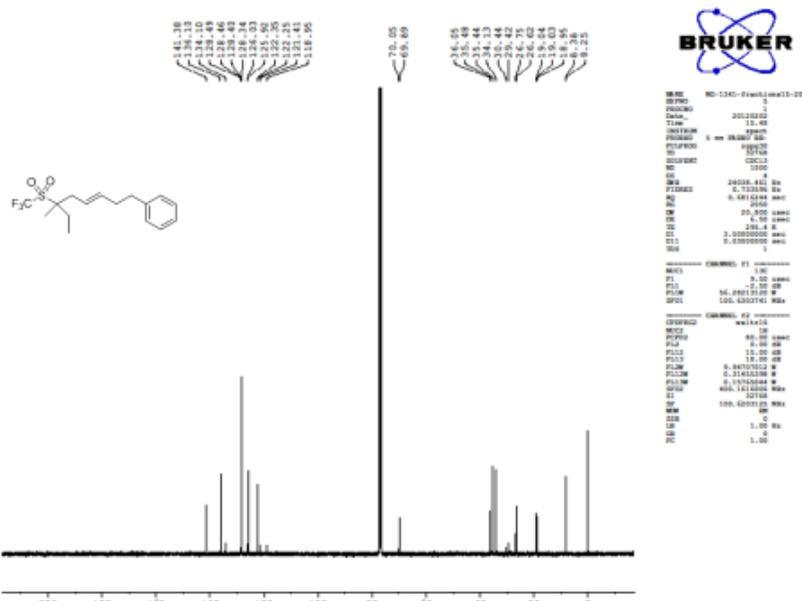


Figure A11: <sup>1</sup>H NMR for (6-methyl-6-((trifluoromethyl)sulfonyl)oct-3-en-1-yl)benzene (2.56)





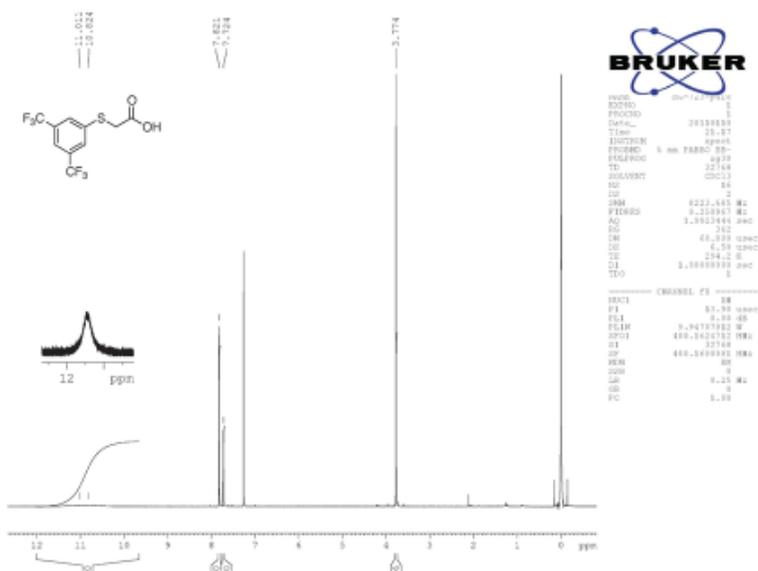
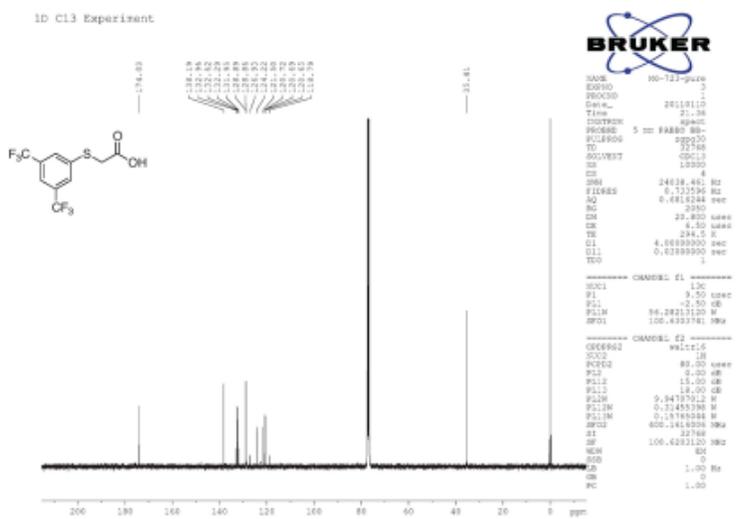


Figure A15:  $^1\text{H}$  NMR for 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetic acid (3.13)





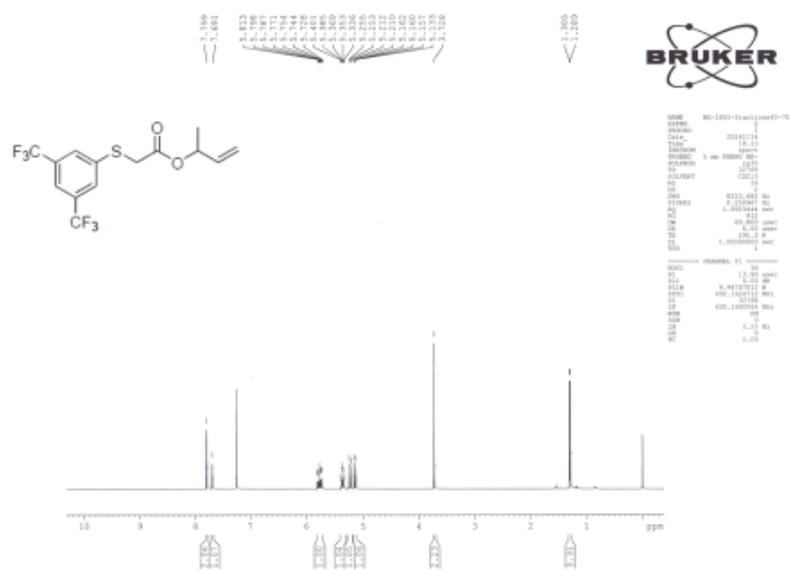




















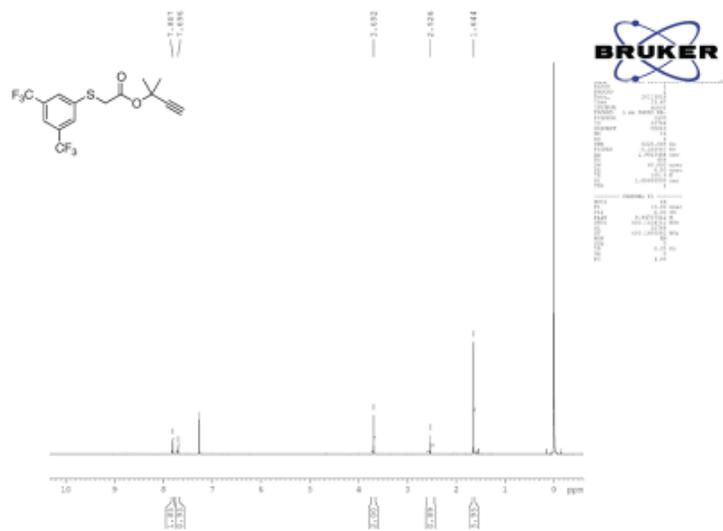


Figure A39: <sup>1</sup>H NMR for 2-Methylbut-3-yn-2-yl-2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.48)

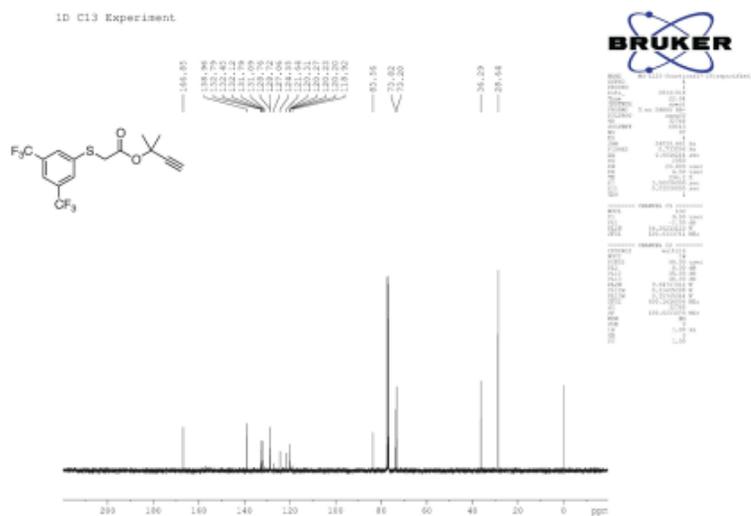


Figure A40: <sup>13</sup>C NMR for 2-Methylbut-3-yn-2-yl-2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate (3.48)





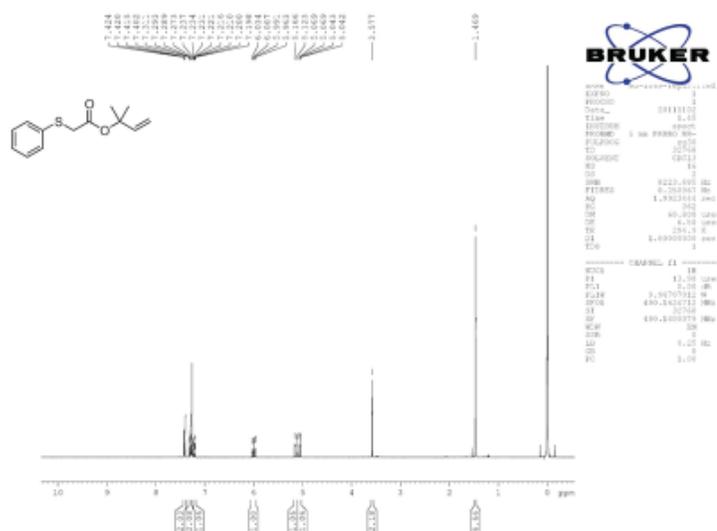


Figure A45: <sup>1</sup>H NMR for 2-Methylbut-3-en-2-yl 2-(phenylthio)acetate (3.55)

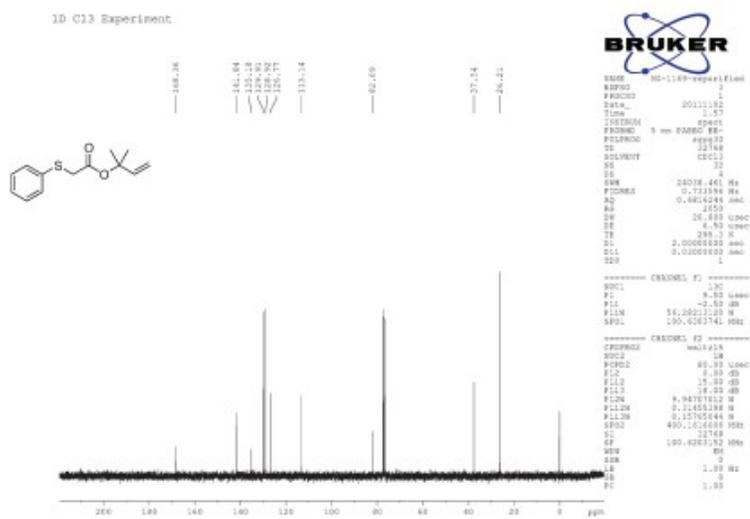


Figure A46: <sup>13</sup>C NMR for 2-Methylbut-3-en-2-yl 2-(phenylthio)acetate (3.55)



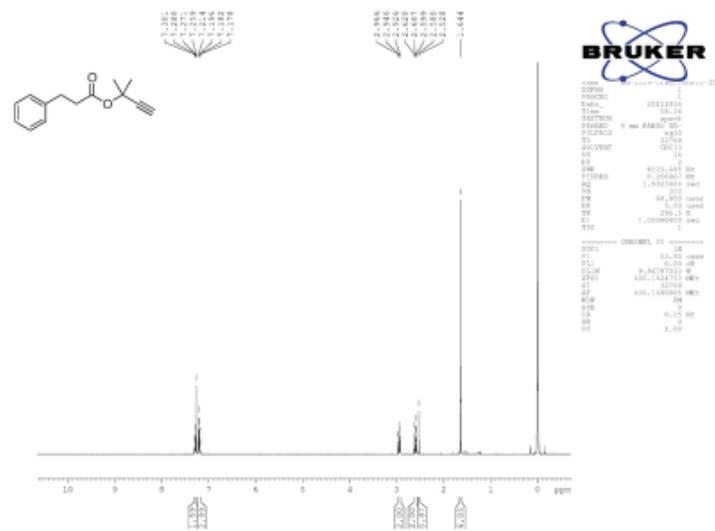


Figure A49: <sup>1</sup>H NMR for 2-Methylbut-3-yn-2-yl 3-phenylpropanoate (3.60)

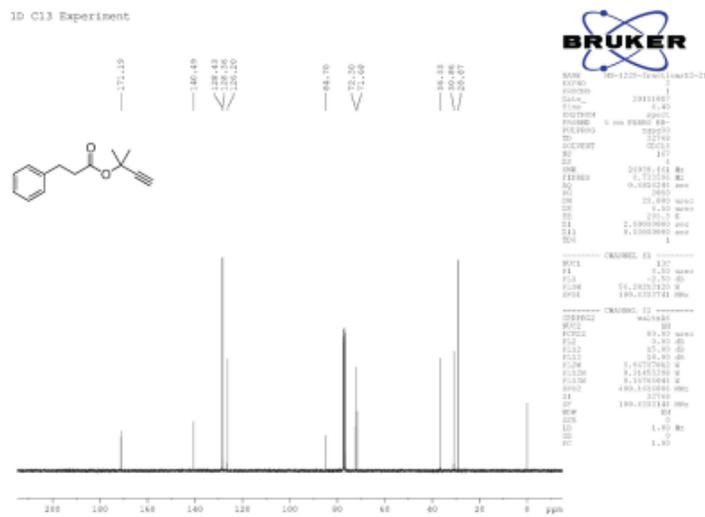


Figure A50: <sup>13</sup>C NMR for 2-Methylbut-3-yn-2-yl 3-phenylpropanoate (3.60)



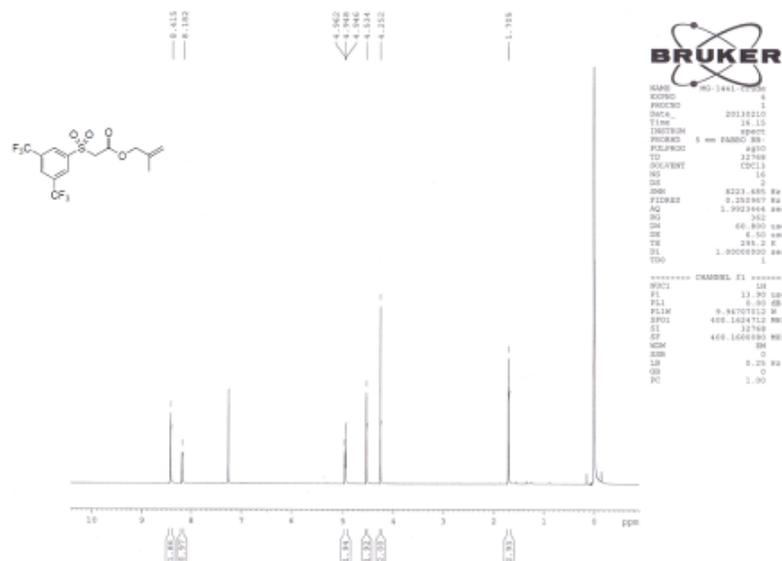


Figure A53: <sup>1</sup>H NMR for 2-Methylallyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.66)

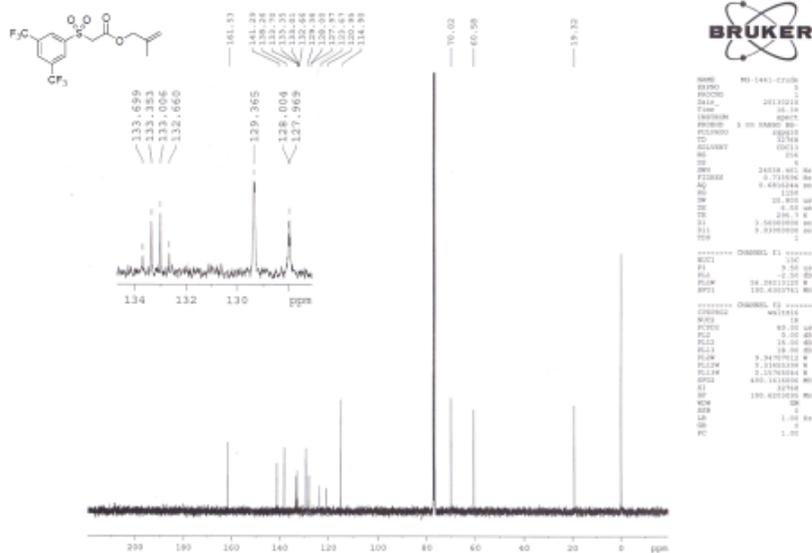


Figure A54: <sup>13</sup>C NMR for 2-Methylallyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate (3.66)









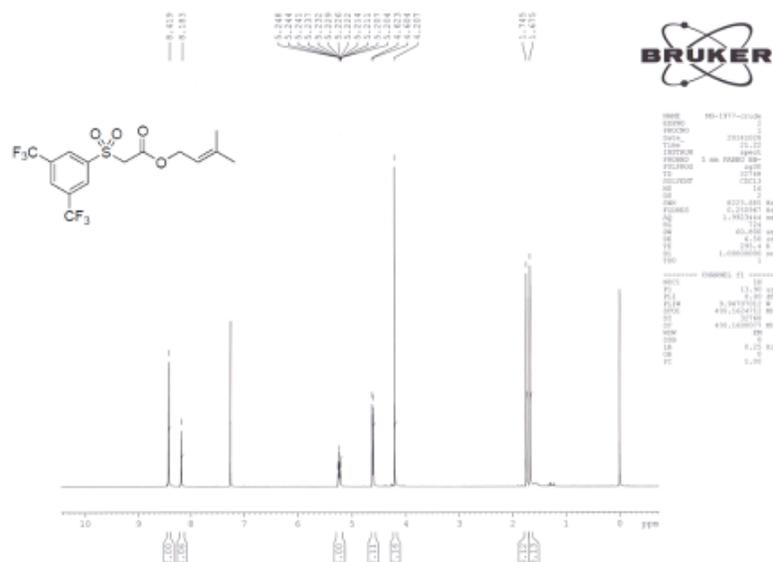
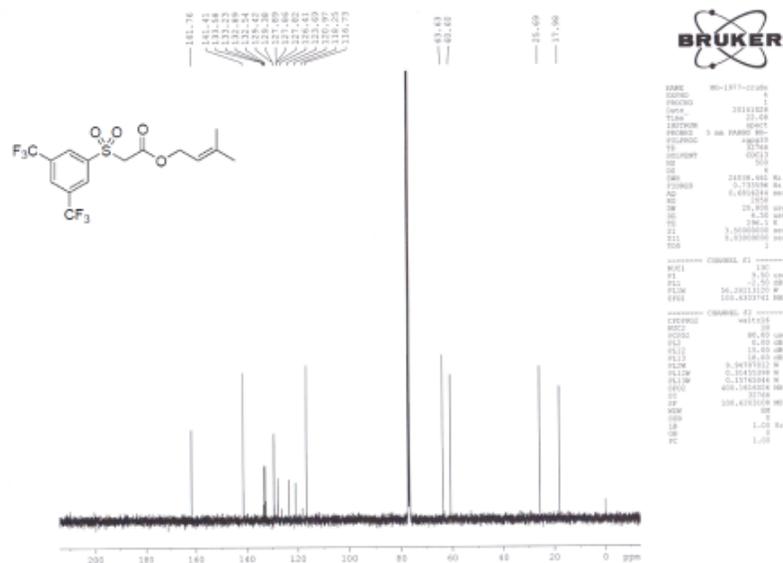


Figure A63: <sup>1</sup>H NMR 3-Methylbut-2-en-1-yl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate for (3.74)









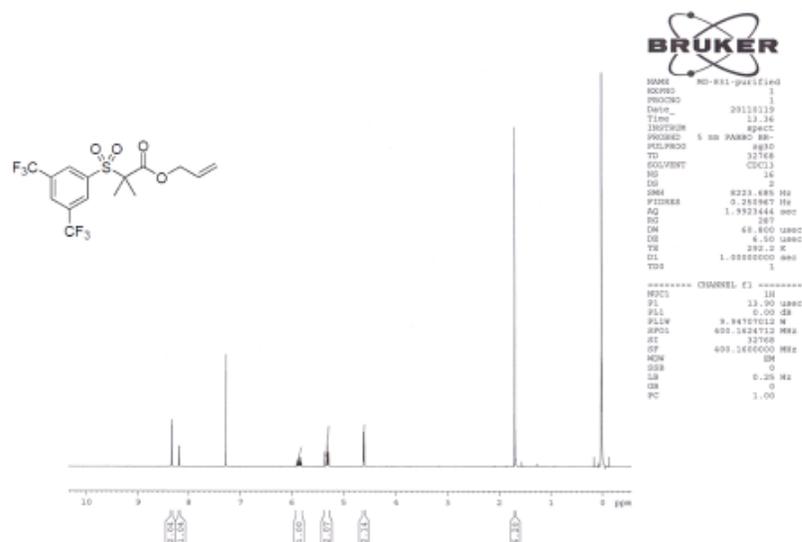


Figure A71:  $^1\text{H}$  NMR for Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-methylpropanoate (3.79)

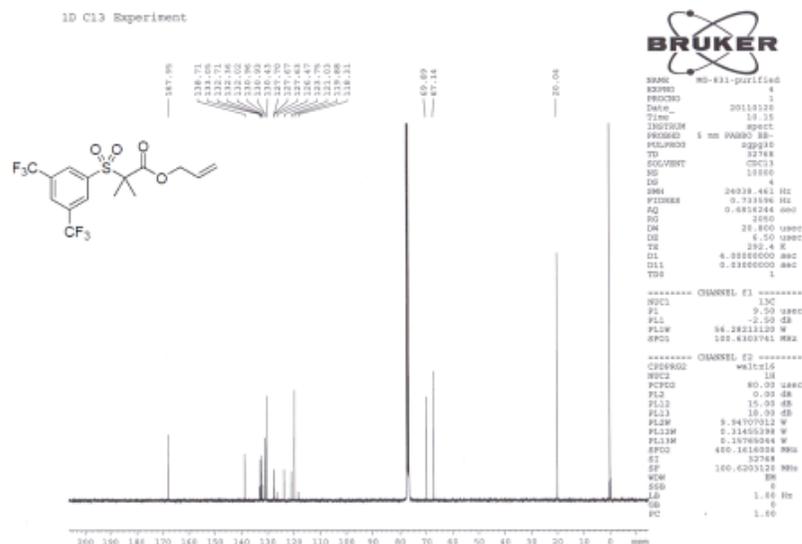


Figure A72:  $^{13}\text{C}$  NMR for Allyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-methylpropanoate (3.79)











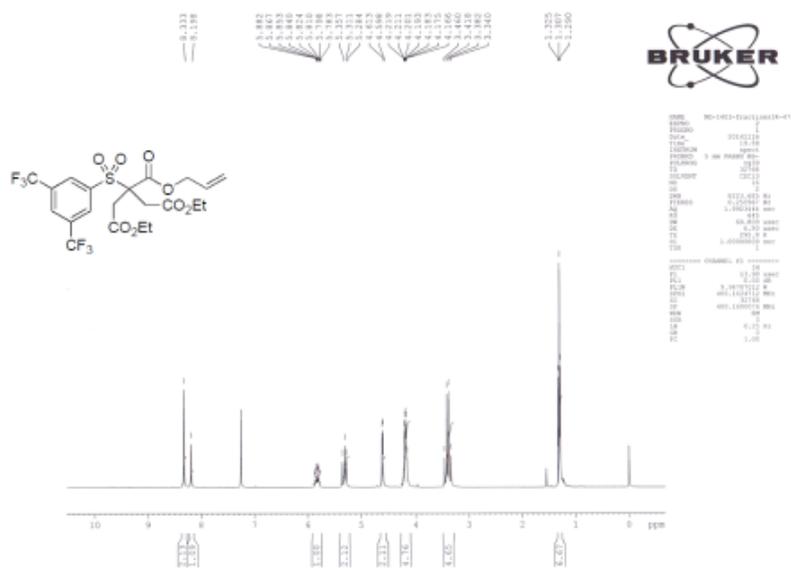


Figure A82: <sup>1</sup>H NMR for 2-allyl 1,3-diethyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)propane-1,2,3-tricarboxylate (3.85)

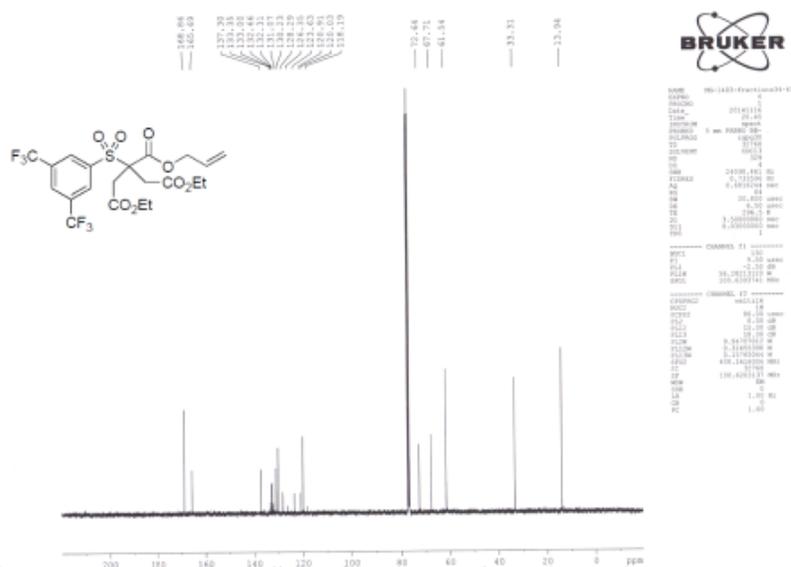


Figure A83: <sup>13</sup>C NMR for 2-allyl 1,3-diethyl 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)propane-1,2,3-tricarboxylate (3.85)

















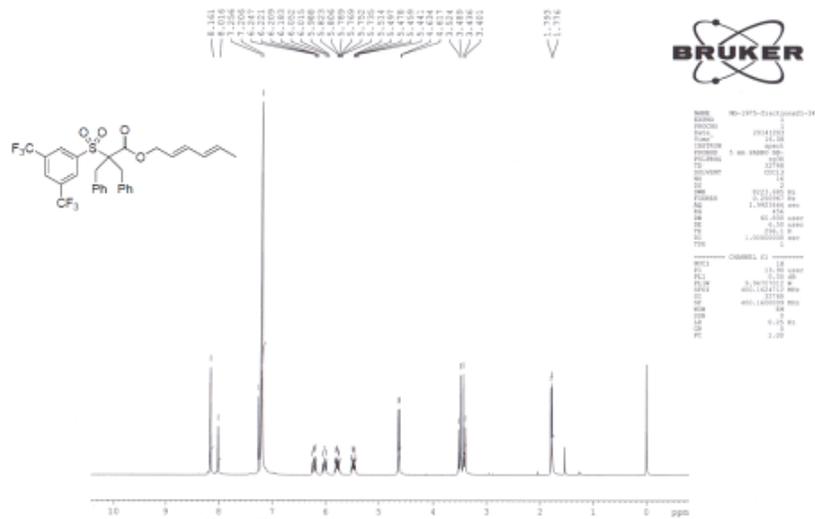


Figure A99: <sup>1</sup>H NMR for (2E,4E)-hexa-2,4-dien-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.94)

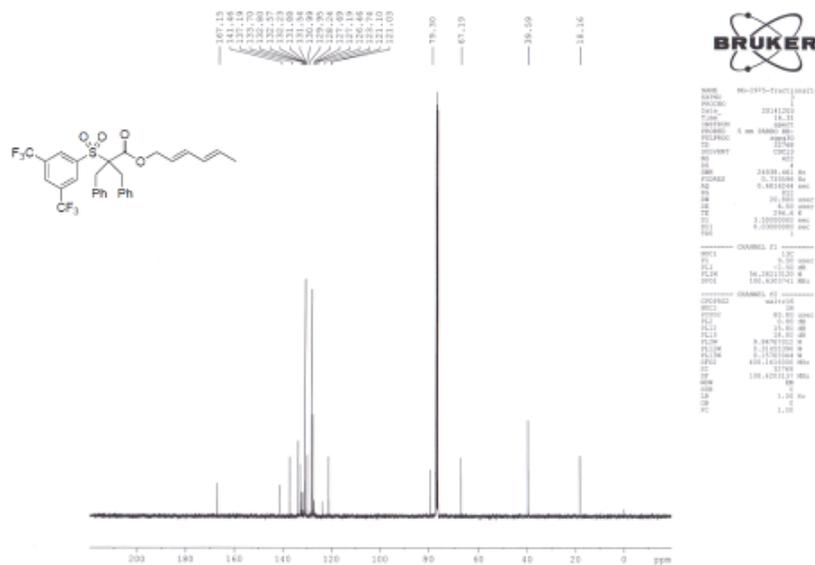
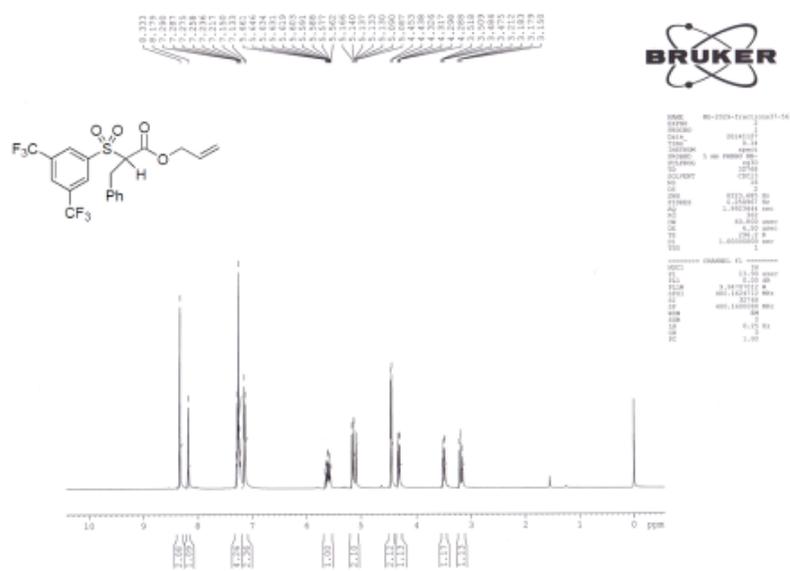


Figure A100: <sup>13</sup>C NMR for (2E,4E)-hexa-2,4-dien-1-yl 2-benzyl-2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)-3-phenylpropanoate (3.94)



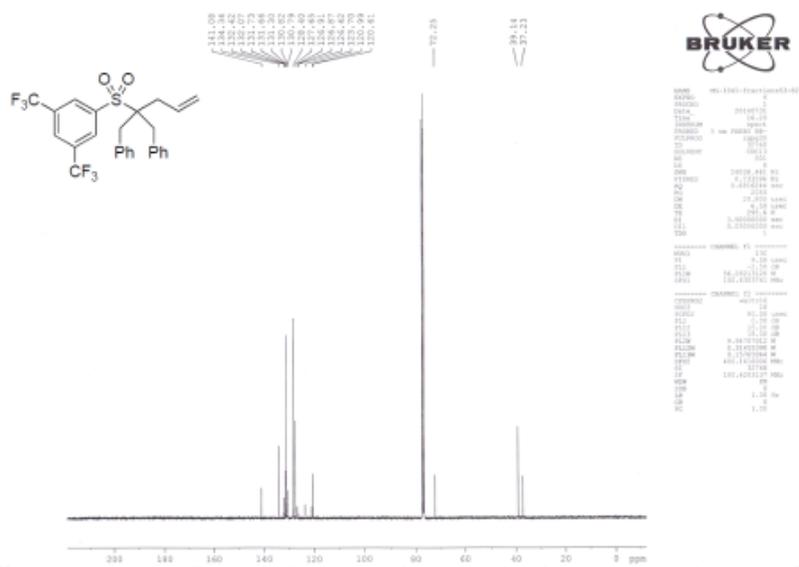
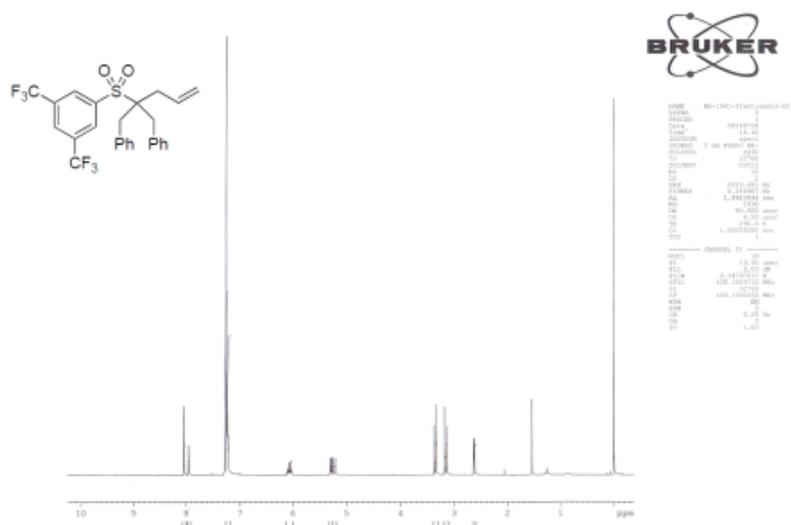




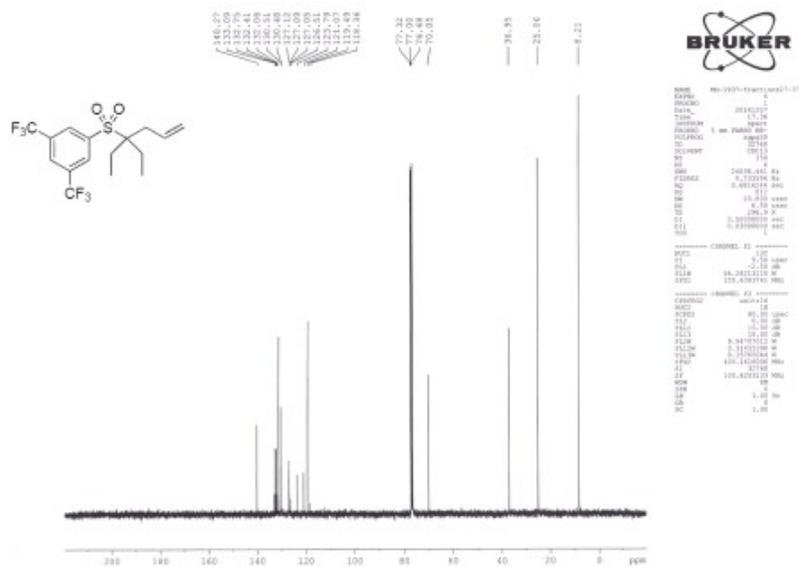
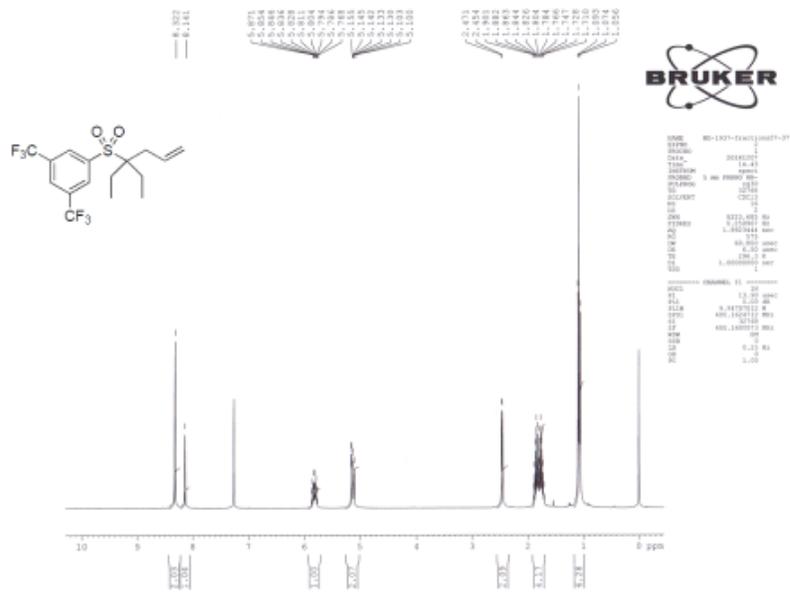














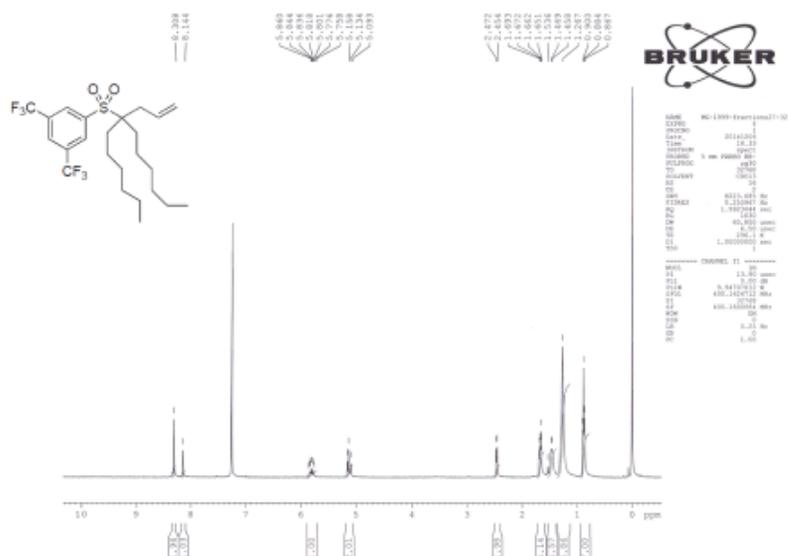


Figure A119:  $^1\text{H}$  NMR for 1-((7-allyltridecan-7-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.128)

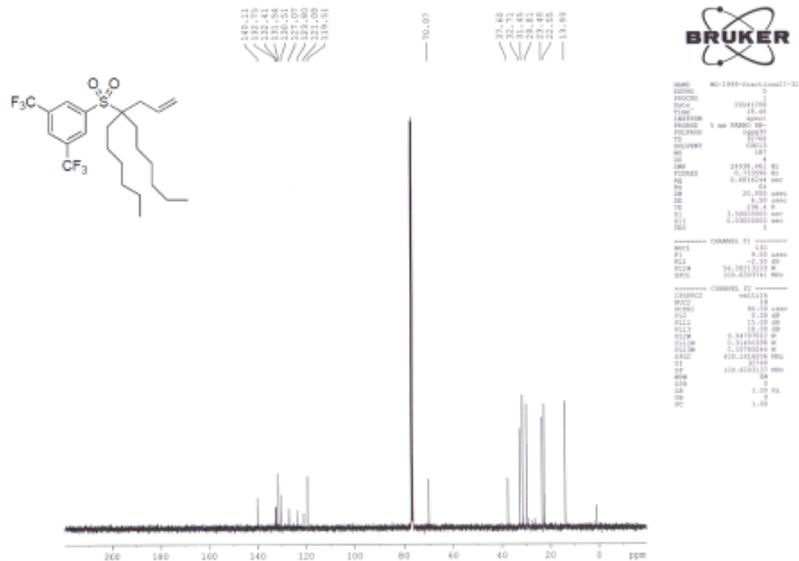


Figure A120:  $^{13}\text{C}$  NMR for 1-((7-allyltridecan-7-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.128)



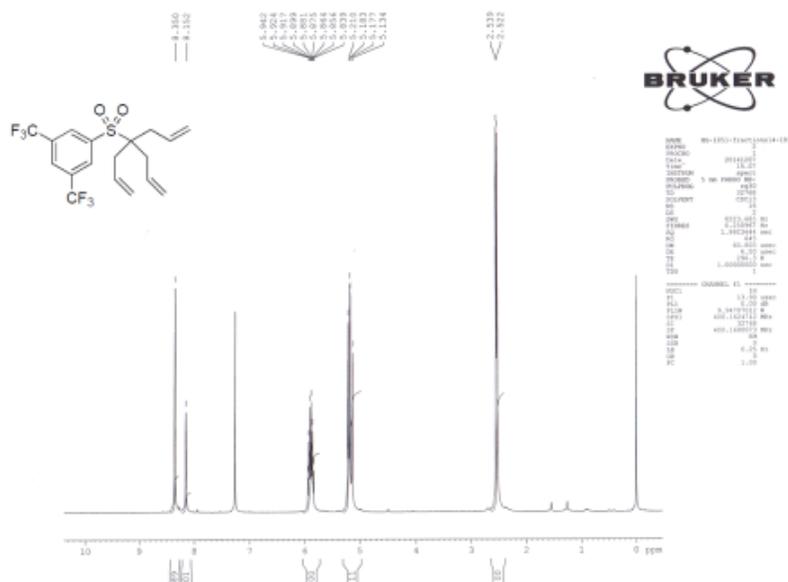
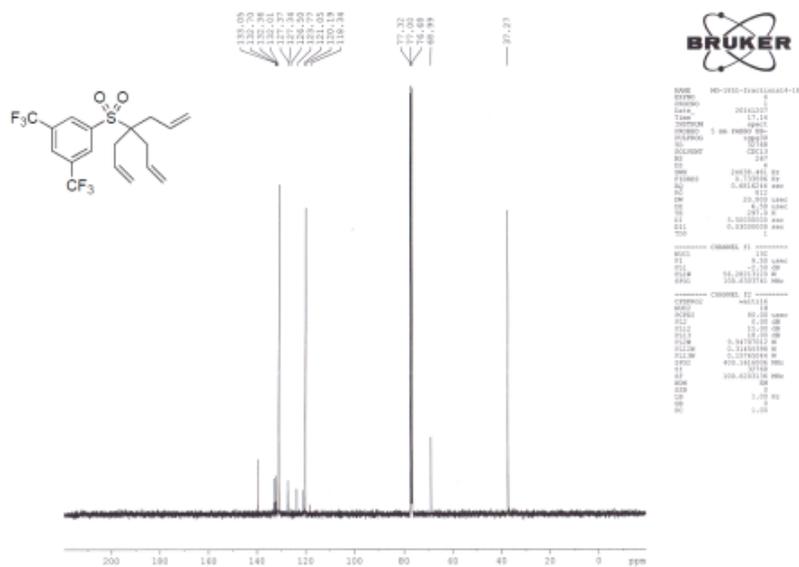


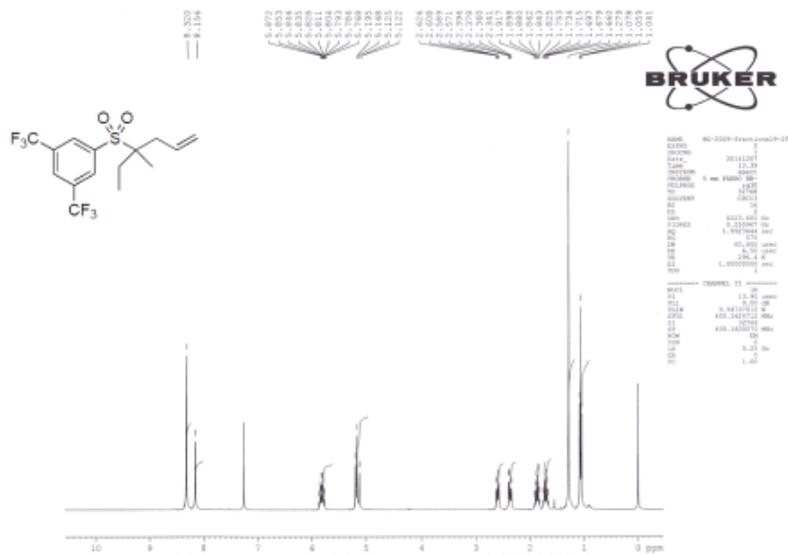
Figure A123:  $^1\text{H}$  NMR for 1-((4-allylhepta-1,6-dien-4-yl)sulfonyl)-3,5-bis(trifluoromethyl)benzene (3.130)



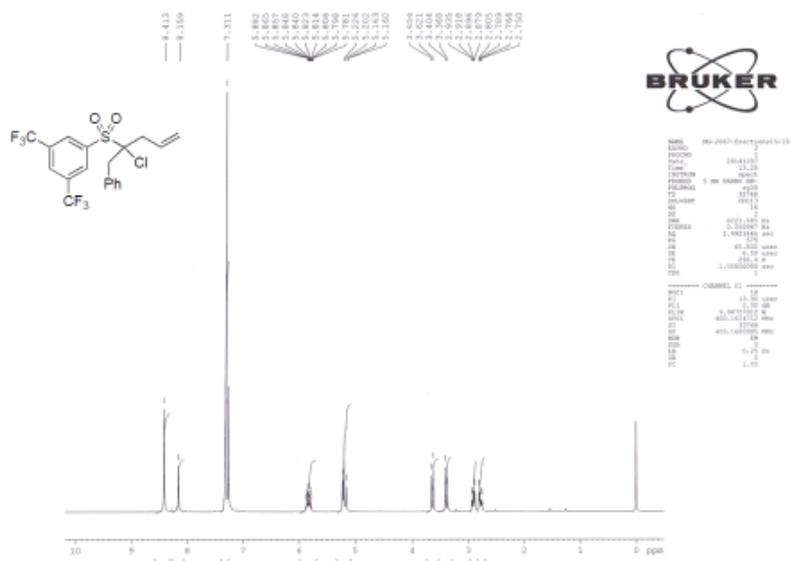


















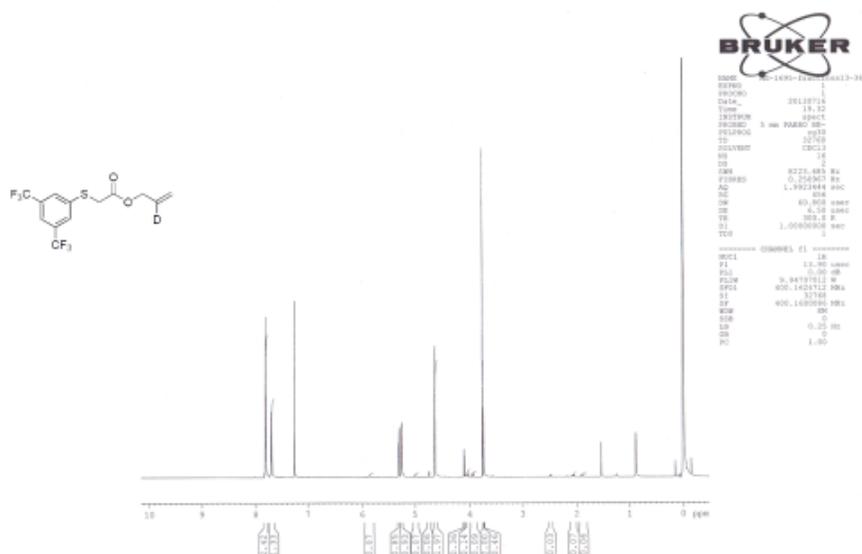


Figure A143: <sup>1</sup>H NMR for Allyl-2-d 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate

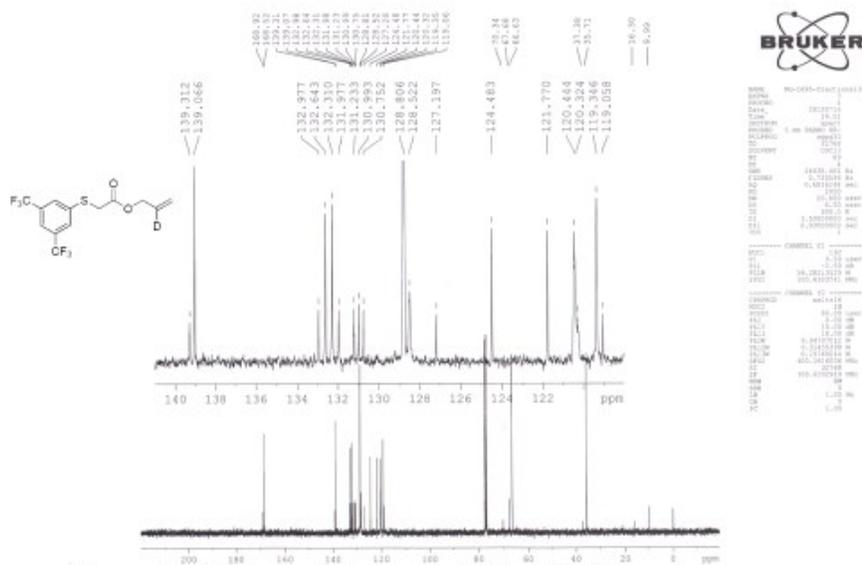


Figure A144: <sup>13</sup>C NMR for Allyl-2-d 2-((3,5-bis(trifluoromethyl)phenyl)thio)acetate

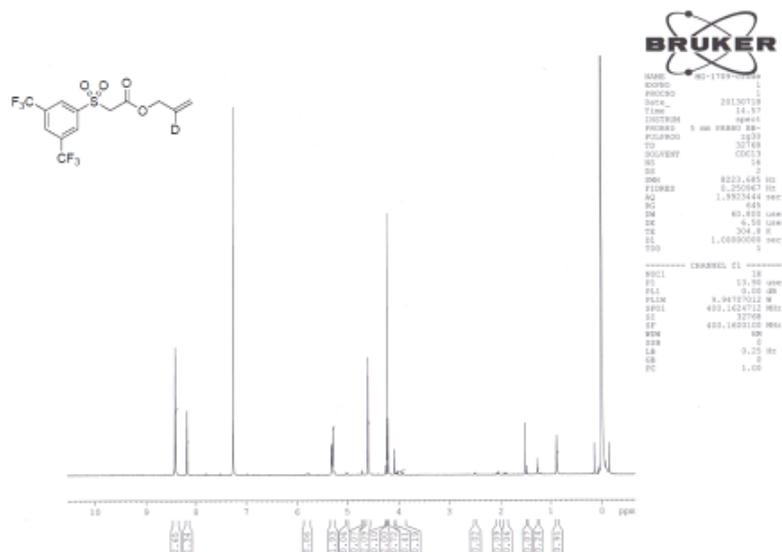


Figure A145: <sup>1</sup>H NMR for Allyl-2-d 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate

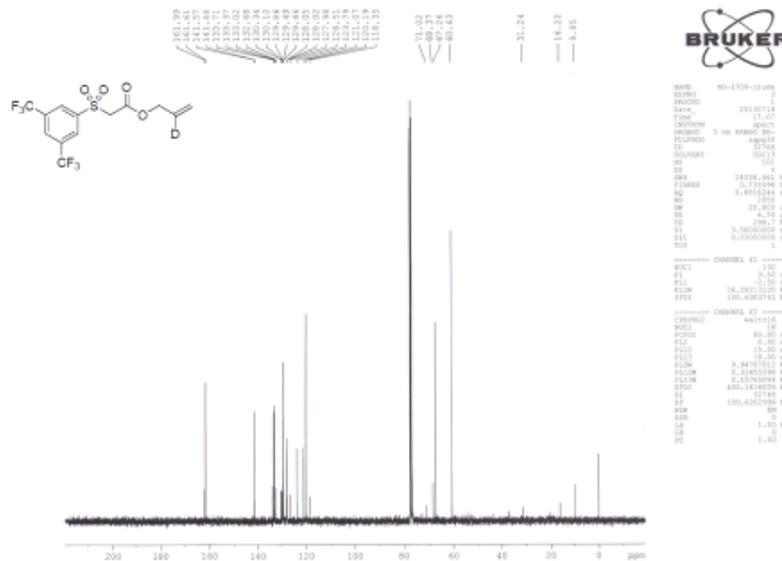


Figure A146: <sup>13</sup>C NMR for Allyl-2-d 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate



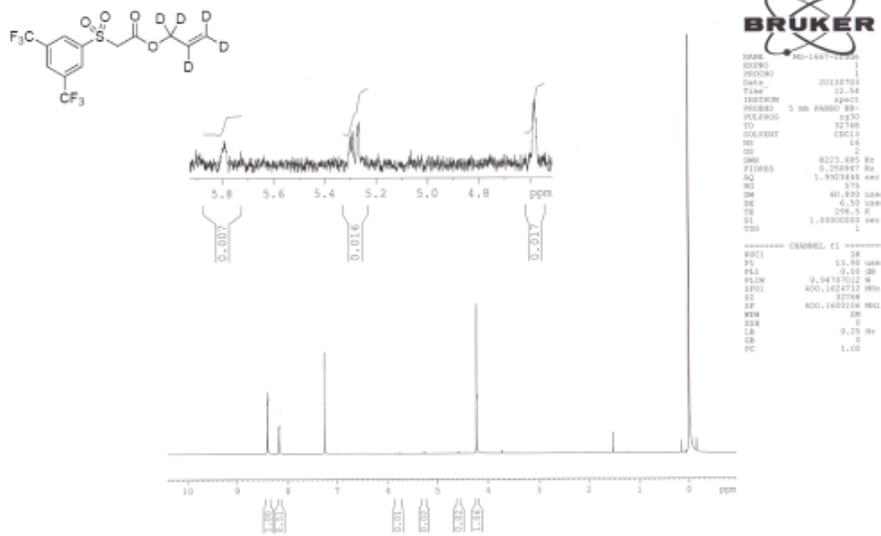


Figure A149: <sup>1</sup>H NMR for Allyl-d<sub>5</sub> 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate

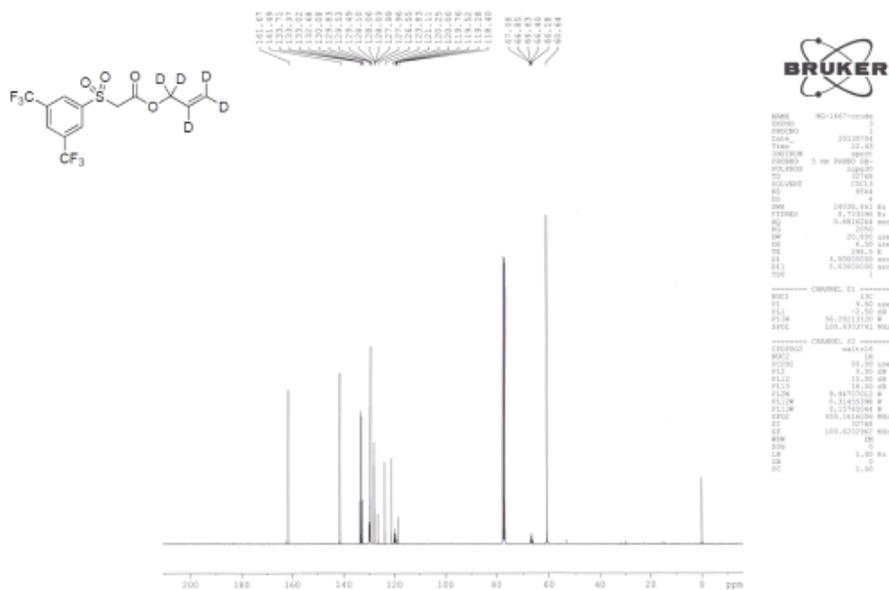


Figure A150: <sup>13</sup>C NMR for Allyl-d<sub>5</sub> 2-((3,5-bis(trifluoromethyl)phenyl)sulfonyl)acetate



