Dedicated to all my wonderful teachers during the years.
Acknowledgements

Phil, thank you for allowing me to join your lab and for the great patience and care you showed me during the years. Your incredible discipline, clarity of mind and purpose have guided me through this journey, even when times were though, the NMRs blurry and the entire world “in shambles”. I could never thank you enough for the support and encouragement you have given me. On a different level, your kind words of advice, but also rigorous critiques have helped me shape my character and identity as a scientist. For all that, I am deeply grateful and I feel incredibly privileged to have had the opportunity to work and learn from you.

The Scripps Research Institute is a outstanding institution that attracts the best young scientists from all over the world. As an international student, I have found a home here and I have been cherished and accepted for my true self, and all those whom I interacted with within this institution, have only had words of encouragement and support and for that I am truly grateful.

During my graduate experience I have had the opportunity to work very independently but also in teams with great chemists. The desaturation project was started as a side idea from the eudesmane project that Dr. Ke Chen worked on. Ke has been my hoodmate for the first two years of graduate school and I am incredibly indebted to her for all her teachings about TLC and reaction monitoring, column chromatography, time management, general lab dynamics and Phil “stuff”. We actually never ended up going shopping, as she had excitedly promised me during the recruiting weekend…

I spent two years working independently on the desaturation project, but ultimately it was finished as a team project. For the past eight months I’ve had the privilege and pleasure
to work with Will Gutekunst, Dr. Abraham Mendoza and Jorge Otero who joined with us for a brief period of three months. As teammates, they brought in fresh ideas, energy, enthusiasm and smarts, and I am very grateful for their efforts and their patience when running some painful pTLCs. I would also want to thank them for their advice on “social” manners and for their friendship.

During the past five years I had the great opportunity to interact with numerous excellent chemists who have spent time in the Baran lab. I am grateful for their advice and discussions on scientific matters, their help with finding chemicals and glassware, their understanding when I was under a serious Lady Gaga spell and could not stop playing her music in lab, for accepting my quirks about the rotovaps, the balance, gloves, clamps etc., but also for being my friends.

My friend Melissa Omand has been a great supporter during grad school. She patiently listened to all my stories about difficult purifications, low yields and she always lifted my spirits and encouraged me to push forward toward the degree I wanted. Rocky is the unofficial member of the Baran lab and “gymming” at Shiley under his guidance has been a great way to burn stress, emotions and fat, while gaining strength and self-confidence. Thank you, Rocky.

Finally, I would like to thank my family for their unparalleled patience and support of my education. Being very far away from home for years in a row has not been easy on any of us, but we made it work. My sister Andreea is best at poking fun at my nerdy life and can always make me laugh. My parents are simple folks and from very early on they have thought me the value of hard work and of living a dignified life. I am deeply grateful to them for all their teachings and unconditional love.
# Table of Contents

## Acknowledgements

## I. Table of Contents

| Section                                           | Page |
|---------------------------------------------------|------|
| I. Table of Contents                              | viii |
| II. List of Tables and Figures                    | x    |
| III. List of Abbreviations                        | xii  |
| ABSTRACT                                          | xvi  |
| 1. Introduction and Background                    | 1    |
| 1.1 Introduction                                  | 2    |
| 1.2 Background and Significance                   | 2    |
| 2. Reaction Development                           | 10   |
| 2.1 Preliminary Results for a Desaturation Reaction | 11  |
| 2.2 The design of a "portable desaturase" and proof of concept | 16  |
| 2.3 Optimization Studies towards a Guided Desaturation Reaction | 19  |
| 2.4 References                                    | 34   |
| 3. Applications                                   | 36   |
| 3.1 Applications of the Desaturation Reaction on Simple Aliphatics | 37  |
| 3.2 Applications of the Desaturation Reaction in Complex Settings | 41  |
| 3.3 References                                    | 45   |
| 4. Mechanistic Investigations                     | 46   |
| 4.1 Mechanistic Studies                           | 47   |
| 4.2 Proposal for the Reaction Mechanism           | 49   |
| 4.3 References                                    | 50   |
Conclusion and Distribution of Credit ........................................................................................................ 51

5. Experimental .......................................................................................................................................... 53

Appendix .................................................................................................................................................. 116

Curriculum Vitae ...................................................................................................................................... 247
II. List of Tables and Figures

Figure 1.1 Existing methodologies for olefin synthesis from pre-oxidized substrates .......................... 3
Figure 1.2 Selected protocols for the desaturation of activated aliphatics ........................................... 4
Figure 1.3 Pioneering studies for alkane desaturation ........................................................................... 5
Figure 1.4 Desaturases in Nature .......................................................................................................... 7
Figure 1.5 Proposed mechanism for desaturation by desaturases ......................................................... 8
Figure 2.1 Initial studies for a direct desaturation reaction using the trifluorethyl carbamate directing group ........................................................................................................................................ 12
Figure 2.2 Preliminary result for desaturation with the trifluorethyl carbamate directing group ................. 13
Table 2.1 Investigations of a desaturation reaction mediated by an amidyl radical ............................... 14
Figure 2.3 Proposed sequence of events for olefin formation at high temperature in the presence of a radical initiator ........................................................................................................................................ 15
Figure 2.4 Precedent for the reactivity of aryl radicals for H-abstraction ................................................. 17
Figure 2.5 Design elements of the "portable desaturase" and proposed series of events for desaturation ........................................................................................................................................ 18
Figure 2.6 Initial investigation to establish an appropriate linker for the "portable desaturase" .................... 20
Table 2.2 Copper salt screening .............................................................................................................. 21
Table 2.3 Solvent screening .................................................................................................................... 22
Table 2.4 Reaction optimization with respect to oxidant loading and reaction temperature ................. 23
Figure 2.7 Preliminary data for the development of a CuBr$_2$-catalyzed desaturation reaction .................... 24
Figure 2.8 Precedent for the reactivity or aryl diazonium salts toward cuprous and cupric salts .............. 26
Figure 2.9 Investigations for the desaturation of a linear aliphatic alcohol........................................28

Table 2.5 Screening of other metal-based oxidants to avoid formation of bromide 2.66.................................................................29

Table 2.6 Additive screening to minimize formation of bromide 2.66.........................................................30

Table 2.7 Testing various amines towards a final structure of the "portable desaturase" .................................................................31

Figure 2.10 Final investigations into the structure of the "portable desaturase".................................................................32

Table 2.8 Final optimization studies and development of final desaturation condition .........................33

Figure 3.1 Synthesis of the “portable desaturase”, Tz’Cl .................................................................37

Figure 3.2 Substrate scope for the guided desaturation reaction .........................................................38

Figure 3.3 Discussing the problems with the linear substrates .................................................................40

Figure 3.4 Applications of the guided desaturation reaction on complex substrates .........................42

Figure 3.5 Substrates which were unproductive during the desaturation reaction ..........................44

Figure 4.1 Experiments to support the proposed 1,7 H-abstraction process .........................................47

Figure 4.2 In situ trapping of the aryl radical ....................................................................................48

Figure 4.3 Mechanistic investigations and proposed reaction mechanism ........................................49
### III. List of Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| DDQ          | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| Pd(TFA)$_2$  | palladium(II) trifluoroacetate |
| DMSO         | dimethyl sulfoxide |
| AcOH         | acetic acid |
| PdCl$_2$     | palladium(II) chloride |
| CuCl$_2$     | copper(II) chloride |
| NaOAc        | sodium acetate |
| MeOH         | methanol |
| C$_6$D$_{12}$ | cyclohexane–d$_{12}$ |
| FeSO$_4$     | iron(II) sulfate |
| Cu(OAc)$_2$  | copper(II) acetate |
| H$_2$O       | water |
| PhH          | benzene |
| NaO'Bu       | sodium tert-butoxide |
| Pd(OAc)$_2$  | palladium(II) acetate |
| AcOBr        | acetyl hypobromide |
| CBr$_4$      | carbon tetrabromide |
| CF$_3$CH$_2$NCO | trifluoroethyl isocyanate |
| PhCF$_3$ (TFT) | trifluorotoluene |
| K$_2$CO$_3$  | potassium carbonate |
| TMP          | 2,2,6,6-tetramethylpiperidine |
| NaOH         | sodium hydroxide |
H₂SO₄  
Ag₂CO₃  
Bipy  
AIBN  
Cu(OTf)₂  
rBuOCl  
I₂  
Pb(OAc)₄  
NOCl  
Cu₂O  
Bu₃SnD  
LAH  
TFA  
CH₃CN (ACN)  
CuF₂  
CuO  
CF₃CH₂OH (TFE)  
DCM  
DME  
CH₃NO₂  
EtCN  
'PrCN  
EtOAc
PhF  fluorobenzene
DMF  dimethylformamide
CCl₄  carbon tetrachloride
CuBr  copper(I) bromide
CuBr(PPh₃)₃  bromotris(triphenylphosphine)copper(I)
CoCl₂•6H₂O  cobalt(II) dichloride hexahydrate
Co(ClO₄)₂•6H₂O  cobalt(II) perchlorate hexahydrate
FeCl₃  iron(III) trichloride
[Cp₂Fe]PF₆  ferrocenium hexafluorophosphate
PPh₃  triphenylphosphine
Phen  phenanthroline
2-Ac-cyclohexanone  2-acetyl-cyclohexanone
DMAP  4-(dimethylamino)pyridine
AgTFA  silver(I) trifluoroacetate
NaTFA  sodium trifluoroacetate
CAN  ammonium cerium(IV) nitrate
PIFA  [Bis(trifluoroacetoxy)iodo]benzene
(NH₄)S₂O₈  ammonium persulfate
Ce(OTf)₄  cerium(IV) trifluoromethanesulfonate
Ce(SO₄)₂  cerium(IV) sulfate
BHT  2,6-Di-tert-butyl-4-methylphenol
TEMPO  2,2,6,6-Tetramethyl-1-piperidinyloxy
4-OH-TEMPO  4-Hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl
| Symbol    | Name                        |
|-----------|-----------------------------|
| TsOH•H₂O  | tosic acid hydrate          |
| H₃PO₄     | phosphoric acid             |
| TfOH      | triflic acid                |
| AZADO     | 2-Azaadamantane-N-oxy       |
| Ad₂NO⁺    | 1,1-Diadamantyl Nitroxide   |
| TON       | turnover numbers            |
| 'BuONO    | tert-butyl nitrite          |
| TEMPO⁺    | 2,2,6,6-tetramethyl-1-oxopiperidin-1-ium |
ABSTRACT

The excision of hydrogen from an aliphatic carbon chain to produce an isolated olefin (desaturation) without over-oxidation is one of the most impressive and powerful biosynthetic transformations for which there are no simple and mild laboratory substitutes. The versatility of olefins and the range of reactions they undergo is unsurpassed in functional group space. Thus, the conversion of a relatively inert aliphatic system to its unsaturated counterpart can open new possibilities in retrosynthesis. In this article, the invention of a directing group to achieve such a transformation under mild, operationally simple, metal-free conditions is outlined. This “portable desaturase” (TzCl) is a bench-stable, commercial entity (Aldrich, cat # L510092) that is facile to install on alcohol and amine functionalities to ultimately effect remote desaturation, while leaving behind a synthetically useful tosyl group.
1. Introduction and Background
1.1 Introduction

Of all the functional groups in the organic chemical space, the olefin must be regarded as one of the most privileged from the vantage point of utility in synthesis. Numerous methods for olefin synthesis have been extensively developed and applied in both academic and industrial sectors. Additionally, alkenes are some of the most versatile chemical entities and significant research has been done to explore their reactivity and to discover new venues for applicability.  

In recent years, the functionalization of ubiquitous C–H bonds has attracted much interest from the synthetic community. The advantages of such an approach for total synthesis are concrete redox, step and often atom economies by avoiding protecting group manipulations and pre-functionalization. However, the inert nature of the C–H bonds as well as the need for selective protocols, remain significant challenges to overcome when implementing this strategy. Our laboratory has been fruitful in providing creative methods in line with this strategy, toward the total synthesis of complex natural products as well as for the selective functionalization of heterocycles. Interestingly, the functionalization of two vicinal C–H bonds in one process, leading to desaturation or olefin formation from alkanes, is less precedent, and it would represent an important advancement in the field. Such a methodology might prove useful for the direct oxidation of complex hydrocarbons, thus providing new routes to natural product synthesis.

1.2 Background and Significance

Tremendous and continuous research effort has been devoted to the development of olefin-forming reactions. Indeed, more than forty name reactions for alkene synthesis are known to the practitioners of organic chemistry (Figure 1.1) while their applications in the
field of natural product synthesis are beyond the countable. Interestingly, most olefin-forming protocols rely on preoxidized starting materials and fall into four main categories: functionalization of ketones or aldehydes (Figure 1.1A); modification of other alkenes (Figure 1.1B); reductive transformations of alkynes (Figure 1.1B) or synthesis by elimination reactions (Figure 1.1C). ⁷

Figure 1.1 Existing methodologies for olefin synthesis from pre-oxidized substrates A. Common olefination reactions requiring the carbonyl functionality B. Functionalization of alkenes and alkynes to substituted olefins C. Olefin synthesis by elimination reaction from alcohol derivatives or halides.

A less explored strategy for olefin synthesis is the direct desaturation of the parent alkane. Within this category, the dehydrogenation of activated aliphatics, generally a more facile process, has been broadly utilized ⁸ and continues to be investigated. For instance, general protocols for the efficient formation of α, β-unsaturated carbonyl compounds are still needed (Figure 1.2A), ⁹ while the direct desaturation of alkenes to produce dienes remains somewhat challenging (Figure 1.2B). ¹⁰ Additionally, strongly oxidizing reagents
such as DDQ are commonly used for desaturation at activated positions (Figure 1.2C),\textsuperscript{11} although ideally such transformations should be performed catalytically. One such example is the intramolecular transfer-dehydrogenation of cyclic amines to provide enamines upon C–H activation with a Co-complex (1.9) (Figure 1.2D).\textsuperscript{12}

![Diagram of desaturation protocols](image)

**Figure 1.2 Selected protocols for the desaturation of activated aliphatics**

A. Recent advancement for the desaturation of \(\alpha\)-to carbonyls. B. One of the rare examples of desaturation of alkenes to dienes. C. A common application of DDQ in total synthesis. D. An example of a Co-catalyzed intramolecular transfer desaturation.

In contrast, the efficient oxidation of unactivated alkanes directly to alkenes remains an unmet challenge and approaches to this problem have only rarely surfaced in methodological studies.\textsuperscript{13} Select examples of reported strategies for alkane dehydrogenation are shown in Figure 1.3. In general, these approaches employ high-energy radicals (Figure 1.3A, B)\textsuperscript{14} or transition metals (Figure 1.3C, D)\textsuperscript{15} to overcome the high thermodynamic stability of the C–H bond. Notably, Breslow’s groundbreaking work awakened the community to the strategic value of a remote desaturation reaction and provided extensive
application on steroid frameworks (Figure 1.3B). An area of great interest has been the development of metal-based catalysts for desaturation. Although a challenging feat, advancements have been made with Ir-derived catalysts such as 1.19 to desaturate simple alkanes such as cyclooctane (Figure 1.3C). The major drawbacks of this methodology are catalyst inhibition by the olefin product, even at low concentrations, and the need for a sacrificial H₂-acceptor such as 1.16, to avoid reduction of the alkene product.

![Diagram of alkane desaturation reactions](image)

**Figure 1.3 Pioneering studies for alkane desaturation.** A. Protocol for dehydrogenation employing peroxide-derived O-radicals. B. Breslow’s pioneering study of a remote dehydrogenation. C. Application of Ir-based catalysts toward the desaturation of cyclic alkanes. D. Example of a Pd-catalyzed guided desaturation reaction.

While these pioneering studies have clarified the difficulties in achieving such a transformation (regiocontrol, product isolation, chemoselectivity), most of these methods lack the generality and practicality required for wide use in complex systems. Important
limitations include the use of inconvenient starting materials (e.g., peroxides), poor substrate scope, overoxidation of the resulting olefin, large substrate excesses or harsh reaction conditions. Therefore, the invention of a broadly applicable, mild protocol to achieve regio- and chemoselective desaturation of unactivated aliphatics remains highly desirable.

Remarkably, Nature is able to use desaturase enzymes to achieve direct, selective and controlled oxidations of hydrocarbons with exquisite precision. These enzymes are involved in important biological processes like fatty acids and vitamin D2 biosyntheses (Figure 1.4A, B). For instance, the in vivo synthesis of vitamin D2 via ergosterol (1.25) requires two different desaturases that perform chemo- and regioselective desaturations. Additionally, desaturation reactions are strategic for the synthesis of important metabolites and natural products in vivo (Figure 1.4C).
Figure 1.4 Desaturases in Nature. A. Vitamin D2 biosynthesis mediated by two different desaturases. B. Fatty acid-like desaturation toward capsaicin. C. Example of an oxidative desaturation towards terpenoid natural products.

The generally accepted mechanism by which desaturations are achieved in Nature comprises a number of discrete steps. These processes are illustrated in Figure 1.5 on a fatty acid substrate and they include (1) C-9 specific alkane hydrogen abstraction; (2) single-electron oxidation of the resulting alkyl radical to a carbocation; and (3) stereoselective loss of a proton to provide olefin 1.36. Inspired by this approach to olefin synthesis, an analogous laboratory process was pursued. Given the inherent difficulty of controlling an intermolecular desaturation, as in the case of enzymes, a protocol was developed involving a directing group that could be appended onto commonly encountered functionalities to guide the dehydrogenation of unactivated alkanes.
1.2 References

(1) To date, Nobel Prizes in Chemistry have been awarded to 13 scientists for the study of olefins in synthesis: i) 1950, Otto P. H. Diels and Kurt Alder “for their discovery and development of the diene synthesis”; ii) 1963, Karl Ziegler and Giulio Natta “for their discoveries in the field of the chemistry and technology of high polymers”; iii) 1979, Herbert C. Brown and Georg Wittig “for their development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis”; iv) 2001, William S. Knowles and Ryoji Noyori “for their work on chirally catalysed hydrogenation reactions” and K. Barry Sharpless “for his work on chirally catalysed oxidation reactions”; v) 2005, Yves Chauvin, Robert H. Grubbs and Richard R. Schrock “for the development of the metathesis method in organic synthesis”; vi) 2010, Richard F. Heck, Ei-chi Negishi, Akira Suzuki, “for palladium-catalyzed cross couplings in organic chemistry”.

(2) Newhouse, T.; Baran, P. S. Angew. Chem. Int. Ed. 2011, 50, 3362.

(3) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. Chem. Soc. Rev. 2009, 38, 3010.

(4) a) Gaich, T.; Baran, P. S. J. Org. Chem. 2010, 75, 4657; b) Bruckl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. Acc. Chem. Res. 2011 ASAP.

(5) Breslow, R. Acc. Chem. Res. 1980, 13, 170.

(6) Gutekunst, W. R.; Baran, P. S. Chem. Soc. Rev. 2011, 40, 1976.

(7) Larock, R. C. Comprehensive Organic Transformations; Wiley: New York, 1999.

(8) Smith, M. B.; March, J. March’s Advanced Organic Chemistry; Wiley: New York, 2007.

(9) Diao, T.; Stahl, S. S. J. Am. Chem. Soc. 2011, 133, 14566.

(10) Susuki, T.; Tsuji, J. Bull. Chem. Soc. Jpn. 1973, 46, 655.

(11) Kürti, L. S.; Czakó, B.; Corey, E. J. Org. Lett. 2008, 10, 5247.

(12) Bolig, A. D.; Brookhart, M. J. Am. Chem. Soc. 2007, 129, 14544.

(13) Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. Chem. Rev. 2011, 111, 1761.

(14) a) Cekovic, Z.; Dimitrijevic, L.; Djokic, G.; Smic, T. Tetrahedron 1979, 35, 2021; b) Breslow, R.; Baldwin, S.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. J. Am. Chem. Soc. 1973, 95, 3251.

(15) a) Gottkler-Schnetmann, I.; White, P.; Brookhart, M. J. Am. Chem. Soc. 2004, 126, 1804; b) Dobereiner, G. E.; Crabtree, R. H. Chem. Rev. 2009, 110, 681; c) Giri, R.; Maugel, N.; Foxman, B. M.; Yu, J.-Q. Organometallics 2008, 27, 1667; d) Baudoin, O.; Herrbach, A.; Guéritte, F. Angew. Chem. Int. Ed. 2003, 42, 5736; e) Johnson, J.
A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900; f) Motti, E.; Catellani, M. *Adv. Synth. Cat.* **2008**, *350*, 565.

(16) a) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146; b) Breslow, R.; Snider, B. B.; Corcoran, R. *J. Am. Chem. Soc.* **1974**, *96*, 6792.

(17) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley: New York, 2009.

(18) Nes, W. D. *Chem. Rev.* **2011**, *111*, 6423.

(19) a) Bennett, D. J.; Kirby, G. W. *J. Chem. Soc. C: Organic* **1968**, 442; b) Prasad, B. C. N.; Kumar, V.; Gururaj, H. B.; Parimalan, R.; Giridhar, P.; Ravishankar, G. A. *PNAS* **2006**, *103*, 13315; c) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532.

(20) a) Shanklin, J.; Cahoon, E. B. *Annu. Rev. Plant Physiol. Plant Molec. Biol.* **1998**, *49*, 611; b) Buist, P. H. *Nat. Prod. Rep.* **2004**, *21*, 249.

(21) a) Kim, C.; Dong, Y.; Que, L. *J. Am. Chem. Soc.* **1997**, *119*, 3635; b) Bigi, M. A.; Reed, S. A.; White, M. C. *Nat Chem* **2011**, *3*, 216.

(22) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.
2. Reaction Development
2.1 Preliminary Results for a Desaturation Reaction

Our interest in a direct desaturation reaction was sparked during the synthesis of the eudesmane terpenes\(^1\) using a cyclase/oxidase synthetic strategy.\(^2\) This synthesis employed a methodology previously developed in our laboratory for 1,3-diol synthesis (Figure 2.1A).\(^3\) In this transformation, a trifluoroethyl carbamate derivative 2.2 is treated with AcOBr to generate a N-Br species 2.3 that reacts under photochemical conditions, in the presence of CBr\(_4\), to give bromide 2.4. An intramolecular S\(_{N1}\) reaction mediated by Ag\(_2\)CO\(_3\) leads to carbonate 2.5, which is finally hydrolyzed to diol 2.6. When applied on the eudesmane derivative 2.7, this methodology morphed into a formal desaturation protocol to give olefin 2.9 (Figure 2.1B). Alkene 2.9 was obtained upon base-mediated elimination of alkyl bromide 2.8 and it allowed access to highly oxidized members of the family: 11-epieudesmantetraol (2.11) and eudesmantetraol (2.12). Given the strategic importance of the olefin functionality in this context and other total syntheses,\(^4\) the invention of a direct desaturation reaction of aliphatics was deemed highly desirable.

Our experience with employing amidyl radicals for C–H abstraction created the opportunity to expand this chemistry to the direct desaturation of aliphatics. The proposed sequence of events is detailed in Figure 2.1C: installation of the directing group and treatment with AcOBr would provide 2.13 which is photochemically labile and generates amidyl radical 2.14 that further undergoes H-abstraction to provide an alkyl radical 2.15. The challenge would be to avoid alkyl radical recombination and instead to promote its oxidation to an alkyl cation such as 2.16, which would eliminate to olefin 2.17. Upon removal of the directing group, a homoallylic alcohol such as 2.18 would result. Indeed, the oxidation of
alkyl radicals to cations by cupric salts and their subsequent elimination to olefins has been extensively described by Kochi, so such a system was investigated first.

After a few trials, it was found that N–Br carbamate 2.20 reacts with Cu(OAc)$_2$ and 2,2′-bipyridine (bipy) at 100 °C, in the presence of catalytic amounts of AIBN to give a complex mixture of products (Figure 2.2). The desired olefin 2.21 was obtained in ~13% yield, while 2.22 was the major product. Small amounts of products resulting from overoxidation (2.24) or side-reactions (2.23 and 2.5) were also detected. Despite the modest outcome, this initial experiment provided proof of concept for a desaturation reaction mediated by a trifluoroethyl carbamate, however more optimization was certainly needed.
Figure 2.2 Preliminary result for desaturation with the trifluoroethyl carbamate directing group.

As shown in Figure 2.2 the good combined yield of 2.21 and 2.22 (~75%) indicated an efficient generation of N-radicals from 2.20, however the low ratio of 2.21:2.22 as well as the formation of byproducts demanded further optimization. The reduction product 2.22 could result from quenching of the N-radical species or the alkyl radical intermediates resulting after intramolecular H-abstraction. However, the amount of 2.22 could not be reduced by changing the solvent (DCE, PhH, PhF, DMF, THF, DME, ethanol, CH$_3$NO$_2$, CH$_3$CN), so the focus turned to accelerating the rate of alkyl radical oxidation. Upon screening various copper-based oxidants, it was found that Cu(OTf)$_2$ provided a better outcome than Cu(OAc)$_2$ (Table 2.1, Entries 1 and 2). Not only did the ratio of 2.21:2.22 increase from 1:5 to 1:1.66, but the formation of byproducts was inhibited. This improvement could be due to the stronger oxidative potential of Cu(OTf)$_2$ compared to Cu(OAc)$_2$ (about an order of magnitude).$^{5c}$

When considering other chelating ligands, 6,6’-dimethyl-bipy and 4,4’-di-tertbutyl-bipy (Entries 3, 4) did not provide any olefin and only the reduced product 2.22 was observed. It is possible that given their substitution pattern, these ligands act as good H-donors and quench the reactive radical intermediates. Consequently, unsubstituted ligands such as 2,2’-bipyrimidine and 2,2’:6’,2’’-terpyridine (terpy) were tested and the results were
positive (Entries 5, 6), with terpy providing a 1:1 ratio of products, in good isolated yield (87%) while the reaction appeared to be scalable and reproducible (Table 2.1, Entry 6). The reaction was further optimized to minimize the amount of AIBN employed. After a few trials, it was found that 0.10 equiv of AIBN (down from 0.25 equiv, Entry 6) was sufficient as long as the temperature was increased to 140 °C (Entry 7). When control experiments were run for this transformation, a surprising reactivity pattern emerged. It appears that olefin formation occurs equally well in the absence of a metal-oxidant (Entry 8) or/and ligand (Entry 9). Clearly, this data indicates a different reaction mechanism than previously assumed and it rules out the possibility that an alkyl cation is involved in the mechanism.

In light of the experimental data, a plausible mechanism for this transformation is described in Figure 2.3: treatment of $\text{2.20}$ with AIBN at elevated temperature might result in

| Entry | Oxidant     | Ligand                  | Temperature (ºC) | Ratio (2.21:2.22) |
|-------|-------------|-------------------------|------------------|-------------------|
| 1     | Cu(OAc)$_2$ | 2,2'-bipyridine         | 120              | 1:5$^b$           |
| 2     | Cu(OTf)$_2$ | 2,2'-bipyridine         | 120              | 1:1.66            |
| 3     | Cu(OTf)$_2$ | 6,6'-dimethyl-bipy     | 120              | only 2.22         |
| 4     | Cu(OTf)$_2$ | 4,4'-di-tert-butyl-bipy| 120              | only 2.22         |
| 5     | Cu(OTf)$_2$ | 2,2'-bipyrimidine      | 120              | 1:1.37            |
| 6     | Cu(OTf)$_2$ | 2,2':6',2''-terpyridine| 120              | 1:1.00$^c$        |
| 7     | Cu(OTf)$_2$ | 2,2':6',2''-terpyridine| 140              | 1:1.00$^d$        |
| 8     | ---         | 2,2':6',2''-terpyridine| 140              | 1:1.25$^d$        |
| 9     | ---         | ---                     | 140              | 1:1.25$^d$        |

Table 2.1 Investigations of a desaturation reaction mediated by an amidyl radical. $^a$Reactions run on 0.027 mmole of $\text{2.20}$. No purification performed since $\text{2.21}$ and $\text{2.22}$ are inseparable by standard chromatography. The product ratio presented is based on $^1$H-NMR integration of the crude mixture after work-up. No carbonate byproducts observed or isolated, unless mentionned. $^b$Other byproducts (see Figure 2.2) form in the reaction and are separated by chromatography. $^c$Reaction run on 13X (0.351 mmole) scale. Product mixture isolated in 87% yield. Ratio of products based on $^1$H-NMR integration of the isolated mixture. $^d$Only 0.10 equiv of AIBN used.
homolytic cleavage of the N–Br bond to form amidyl radical 2.26 which could get quenched by a H-donor to give 2.22 or undergo 1,6 H-abstraction to give alkyl radical 2.27. Under the reaction conditions, 2.27 could react in two different ways: (1) recombination with Br• present in the solution mixture, to give alkyl bromide 2.23 that thermally eliminates to olefin 2.21; (2) abstraction from a H-donor (e.g. PhCF₃, 2.20) to produce carbamate 2.22.

The unfortunate outcome of this study demanded a reevaluation of our approach to desaturation. Although the trifluoroethyl carbamate directing group provides access to amidyl radicals capable of H-abstraction at unactivated sites, the major limitation associated with this protocol was the need for strongly oxidizing reagents (e.g. tBuOCl, AcOBr, I₂/Pb(OAc)₄, NOCl etc.) required to initially activate the N-center.⁶ The resulting N-derivatives decompose efficiently to N-centered radicals and other reactive radical byproducts (e.g. Br•) that are highly prone to recombination side reactions (e.g. in situ formation of alkyl bromide 2.23) thus significantly affecting the selectivity of the reaction. Given these difficulties, a drastically new approach to desaturation was needed. With the belief that our overall strategy to dehydrogenation inspired by desaturases was sound, the challenge became identifying a highly reactive radical species for H-abstraction, to be
generated under mild conditions to allow a chemoselective transformation. Thus, the invention of a new directing group capable of affecting the desaturation of aliphatics was necessary.

2.2 The design of a “portable desaturase” and proof of concept

Three basic criteria were taken into account when designing a new directing group for desaturation (“portable desaturase”): (1) reactivity – the employment of a highly reactive species capable of controlled H-abstraction; (2) practicality – short, scalable synthesis and stability; (3) ease of installation and versatility of the resulting functionality. When considering the reactivity criterion, aryl radicals\(^7\) were identified as highly reactive, very short-lived intermediates (rate of H-abstraction by aryl radicals is on the order of \(10^6 \text{ M}^{-1} \text{s}^{-1}\)),\(^8\) which have rarely been employed in C–H functionalization reactions. Indeed, early reports by Cohen detailed H-abstraction events by aryl radicals at activated sites (\(\alpha\)- to N) to afford demethylation of amides such as \(2.28\) (Figure 2.4A),\(^9\) while Weinreb explored this reactivity for the synthesis of \(\alpha\)-methoxy pyrrolidine derivatives such as \(2.35\) (Figure 2.4B).\(^10\) Interestingly, de Mesmaeker considers naphthyl amine \(2.36\) to study the radical translocation of aryl radicals to alkyl radicals and their subsequent deuterium-trapping (Figure 2.4C).\(^11\) Despite the poor selectivity for H-abstraction, naphthyl radicals are reactive enough to functionalize unactivated methylene C–H bonds (e.g. \(2.40\) and \(2.41\)). Moreover, Pines describes the first example of aryl radicals employed as tools for desaturation (Figure 2.4D, \(2.46\) and \(2.49\)), albeit at an activated position (C–H bond \(\alpha\) to a heteroatom - roughly 7-9 kcal/mol weaker that a 3º C–H bond).\(^12\) Notably, the linker connecting the aryl radical with the aliphatic moiety influences the yield of the reaction and the product distribution (e.g. sulfonamide \(2.41\) vs. amide \(2.48\) in Figure 2.4D).
Figure 2.4 Precedent for the reactivity of aryl radicals for H-abstraction. A. Intramolecular H-abstraction leading to an iminium ion and subsequent demethylation. B. Intramolecular methoxylation of cyclic amides. C. Radical transposition to alkyl radicals and deuterium-trapping. D. Original report of an aryl radical-mediated desaturation at an unactivated position.

Notwithstanding the poorly investigated and highly promiscuous reactivity toward C-H bonds, the use of aryl radicals in synthesis is limited by rather impractical methods for their generation. The most common precursors to aryl radicals are the corresponding diazonium salts \(^7\) (e.g. 2.28, 2.32, 2.41 and 2.48 in Figure 2.4) however, given their intrinsic instability, such species are undesirable starting materials. Alternatively, aryl radicals can be generated upon treatment of the corresponding halides with tin radicals (Figure 2.4C), but
given their toxicity, such reagents are not desirable. Interestingly, an efficient, but underutilized tactic for generating aryl radicals is the reductive dissociation of aryl triazenes\textsuperscript{13} in the presence of acid and catalytic metal salts.\textsuperscript{14} Traditionally used as protecting groups for anilines\textsuperscript{15} and linkers in solid-phase synthesis,\textsuperscript{16} aryl triazenes can be prepared in high yields from the corresponding anilines and are stable to basic, reductive (e.g. LAH) and alkylating conditions, even in complex settings.\textsuperscript{17}

Thus, having decided upon aryl triazenes as potentials tools for C-H functionalization, the proposed set of events for a guided desaturation with a “portable desaturase” is outlined in Figure 2.5. After installing the directing group onto the desired substrate to give B, treatment with acid in the presence of a single-electron reductant would provide an aryl radical C via an aryl diazonium intermediate. This inherently high-energy radical could abstract a proximal hydrogen atom to generate a lower energy alkyl radical D that could be oxidized to a carbocation E and finally terminated to the desired alkene F. Additionally, if a suitable metal salt could participate in both the reduction and oxidation steps, a redox cycle could be envisioned to allow for catalysis.\textsuperscript{18} The final design element involves the directing group transforming into a common protecting group to be easily removed or further elaborated.

\textbf{Figure 2.5} Design elements of the “portable desaturase” and proposed series of events for desaturation
2.3 Optimization Studies towards a Guided Desaturation Reaction

In order to append an aryl triazene onto alcohols and amines, a few common linkers were first investigated. It was found that in the presence of trifluoroacetic acid (TFA) and stoichiometric amounts of CuBr$_2$ (as preceded by Pines,\textsuperscript{19} Figure 2.4D), sulfonate ester 2.50 uniquely gave desaturated product 2.51 in good yield while triazene ester 2.54 and triazene ether 2.57 were unproductive (Figure 2.6). Possible reasons for the observed differences in reactivity could relate to linker angles, bond lengths and bond rotational energies of the species involved in the transition state. In light of previous reports describing intramolecular H-abstractions by aryl radicals (Figure 2.4), these results do not exclude the possibility that the ester and ether linkers might be efficient handles toward desaturation on other aliphatics, however this possibility was not been investigated further. As a result of these preliminary studies, triazene benzenesulfonyl chloride 2.59 became the starting point for the development of a “portable desaturase” and corresponding reaction conditions for desaturation.
The development of a desaturation reaction with a “portable desaturase” centered on solving difficulties associated with the use of aryl radicals. A first task was to inhibit the observed Sandmeyer reaction leading to inseparable aryl halide byproducts (e.g. 2.52). As if a sign for the difficulties ahead, the preliminary set of conditions that provided a good yield of 2.51 (Figure 2.6, eq. 1), were ineffective on the cyclopentyl-ethanol derivative 2.60 (Table 2.2, Entry 1). However, the poor result on 2.60 was viewed as an opportunity to learn more about the reaction and 2.60 was chosen as a pilot substrate for further optimization. When other copper salts were tested (Table 2.2), copper halides led to inseparable mixtures of products (Entries 1–3). Interestingly, both CuF$_2$ and CuO provided olefins without the Sandmeyer byproduct 2.62 (Entries 4, 5), and although they were further investigated in later trials, overall these two oxidants did not show desirable reproducibility or substrate scope. Finally, Cu(OTf)$_2$ afforded an acceptable product yield and a good ratio of 2.61:2.63 = 10:1 (Entry 7), so the investigation of this reaction continued with Cu(OTf)$_2$ as the oxidant.
Table 2.2 Copper salt screening. Isolated yield, ratio determined by integration of the $^1$H-NMR spectrum of the purified mixture; The chloro-analog of 2.62 formed instead.

Having found a way to avoid the Sandmeyer process, this reaction needed further optimization to improve the product yield and to minimize formation of the reduction product 2.63. With this purpose in mind, a number of solvents were screened (Table 2.3). Using a non-polar solvent such as PhH (Entries 1), as well as the more polar CF$_3$Ph, TFE and DCM (Entries 2–4), minimal amounts of product were detected in a complex mixture of other unidentifiable products. Nitrile solvents produced an increasing amount of reduction product depending on the number of available hydrogen atoms in the solvent molecule (Entries 5–7). Not surprisingly, DME acts as a very good H-donor and 2.63 was obtained as the major product in a mixture isolated in 82% yield (Entry 10). Despite the low olefin ratio, this result indicated an efficient formation of the aryl radical intermediate. Although this screening provided some information about the reaction mechanism, none of the solvents investigated was superior to CH$_3$NO$_2$ which gives the highest 2.61:2.63 ratio (10:1, Entry 8) and despite the modest product yield, it remained the solvent of choice for this reaction.
Table 2.3 Solvent screening. Isolated yield, ratio determined by integration of the $^1$H-NMR spectrum of the purified mixture.

Before attempting further optimization of the reaction yield, the possibility of a catalytic reaction was first tested. It was found that turnovers could be achieved when 0.10 equiv of Cu(OTf)$_2$ was used (Table 2.4, Entry 4). Unfortunately, the reaction reaches a plateau at $\sim$ 40% yield independent of the amount of oxidant present (Entries 1–3). When no oxidant is present, non-productive decomposition of the starting material is observed (Entry 5). Despite the poor product yield, the temperature effect on the reaction outcome was investigated to discover that temperatures below 60 °C led to a significant decrease in reaction yields (Entries 7–9). At room temperature the reaction is sluggish with minimal amounts of product observed in the crude mixture.
Table 2.4 Reaction optimization with respect to oxidant loading and reaction temperature. \(^a\) Isolated yield, ratio determined by integration of the \(^1\)H-NMR spectrum of the purified mixture. \(^b\) Reaction allowed to proceed for 5h at rt.

| Entry | \# Cu(OTf)_2 (equiv) | Temperature (ºC) | Yield (% (2.61 : 2.63)) |
|-------|----------------------|------------------|-------------------------|
| 1     | 1.00                 | 80               | 40 (10 : 1)             |
| 2     | 0.50                 | 80               | 42 (7.1 : 1)            |
| 3     | 0.25                 | 80               | 32 (7.1 : 1)            |
| 4     | 0.10                 | 80               | 27 (6.6 : 1)            |
| 5     | ---                  | 80               | decomp                  |
| 6     | 0.25                 | 60               | 36 (7.1 : 1)            |
| 7     | 0.25                 | 50               | 21 (4 : 1)              |
| 8     | 0.25                 | 40               | 21 (2.5 : 1)            |
| 9     | 0.25                 | 25               | < 5 % of 2.61*          |

Adding to a difficult situation given the modest product yield, was the discovery that the set of conditions developed so far [Cu(OTf)_2 (0.25 equiv), TFA (2 equiv), CH_3NO_2 (0.025 M), 60 ºC], was not applicable to other substrates. Indeed, menthol derivative 2.50 and a substrate derived from a linear aliphatic alcohol, 2.64, resulted in decomposition when submitted to those reaction conditions (Figure 2.7, eqs. 1, 3). It then became clear that the study of this reaction could not be advanced using Cu(OTf)_2 as the oxidant and our focus switched to refining a previous set of conditions that employed CuBr_2 which had more general applicability despite the product mixtures obtained. The goal was to investigate the possibility of using this oxidant catalytically (to minimize the Sandmeyer side reaction) and to find an additive or ligand to improve efficiency and product yield.

Indeed, when treated with substoichiometric amounts of CuBr_2 (0.25 equiv) in the presence of acid (TFA, 2 equiv), menthol substrate 2.50 could be desaturated in good yield with minimal amounts of Sandmeyer byproduct 2.52 forming (Figure 2.7, eq 2). The same set of conditions could be applied on 2.64, to obtain olefin 2.65 in a mixture with alkyl
bromide 2.66 (Figure 2.7, eq. 4). This reaction also produced acetamide 2.67 (~10%) via a Ritter-type process with the solvent (CH$_3$CN). For both 2.50 and 2.64, the use of acetonitrile as a solvent was required since CH$_3$NO$_2$ led to rapid substrate decomposition. Although the Ritter side reaction observed for 2.64 indicated an intrinsic instability of the starting material under the reaction conditions, no direct attempts were made to eliminate this byproduct and our main focus remained improving the dehydrogenation process. Formation of an alkyl bromide during desaturation (2.66) has not been observed in other substrates (e.g. 2.50 or 2.60) so it became relevant to understand more about the reaction mechanism in order to inhibit its formation. Thus, with the ultimate goal of identifying a broadly applicable set of conditions for desaturation, optimization of this reaction continued using 2.64 as pilot substrate.

![Figure 2.7](image-url)

**Figure 2.7 Preliminary data for the development of a CuBr$_2$-catalyzed desaturation reaction**

*When CH$_3$NO$_2$ is used instead only decomposition is observed. *$^\text{b}$*Isolated yield, ratio determined upon integration of the $^1$H-NMR spectrum of the purified mixture.*
An initial step in the newly identified research direction was to rule out the possibility that olefin 2.65 would form in situ by elimination from alkyl bromide 2.66 (vide supra). Thus, since 2.65 and 2.66 could not be easily separated by common chromatography procedures, a purified mixture of 2.65 and 2.66 was resubmitted to the reaction conditions to find that the amount of bromide 2.66 increased. This data could be interpreted in two ways: (a) the olefin product either decomposes or partially reacts with CuBr\(_2\) to produce more 2.66, while (b) the presence of 2.66 in the final reaction mixture points to its stability under the reaction conditions. It was thus inferred that formation of 2.65 by elimination from 2.66 is unlikely.

When considering a possible reaction mechanism for this reaction, Kochi’s work on the interaction of aryl and alkyl radicals with cupric salts is suggestive.\(^{21}\) In the common Sandmeyer and Meerwein reactions (Figure 2.8), aryl radicals are generated upon the reductive decomposition of aryl diazonium salts in the presence of catalytic amounts of Cu\(^1\) salts. Indeed, Cu(I) salts are exceedingly effective for this process given the matched oxidation potential with that of diazonium ions.\(^7\) As a result of this interaction, Cu(II) species are formed which efficiently engage in ligand-transfer processes to provide halide products.\(^7\) Interestingly, in the Meerwein arylation the ligand-transfer happens from a proposed Cu(III)-alkyl intermediate (Figure 2.8).\(^{22}\)
Indeed, both the Sandmeyer and Meerwein reactions require catalytic amounts of Cu(I) to promote aryl radical formation, however these reaction can proceed equally well or better, when Cu(II) salts are utilized instead.\textsuperscript{7} Given our empirical data suggesting that CuBr (\textit{vide infra} Table 2.5, Entries 1 and 2) is not as efficient as CuBr\textsubscript{2} in the desaturation reaction, we sought to understand the role of the metal salt. Interestingly, Kochi and others propose that when Cu(II) are employed for the Sandmeyer and Meerwein reaction, limited amounts of Cu(I) species are formed \textit{in situ} which then catalyze the decomposition of the diazonium salts and are regenerated upon a second reduction, at the end of the reaction.\textsuperscript{18b} Thus, an efficient Cu\textsuperscript{I}-Cu\textsuperscript{II} cycle takes place, despite the initial addition of Cu\textsuperscript{II} salts. A proposal for the reduction of a Cu\textsuperscript{II}X\textsubscript{2} (X = Cl, Br) \textit{in situ} is described by Kochi for the Meerwein arylation (Figure 2.8). It was shown that acetone (the solvent of choice for the reaction) reacts to form α-halo-acetone while a transient Cu\textsuperscript{I}X species is produced.\textsuperscript{23} Interestingly, acetonitrile does
not reduce CuX₂. Given this precedent, we sought to find further evidence to explain the formation of aryl radicals under our reaction conditions.

Although the decomposition of aryl diazonium salts requires catalytic amounts of a reductive metal salt, the generation of aryl radicals from aryl triazenes can be accomplished simply with a strong acid at 60–80 °C. Thus, the proposed mechanism to explain formation of olefin 2.65 and alkyl bromide 2.66, as well as the role of CuBr₂, is described in Figure 2.9A. The reaction of 2.64 with TFA would unmask diazonium salt 2.69 which could decompose to aryl radical 2.70 under the reaction conditions (80 °C) or in the presence of catalytic amounts of CuIBr. The short-lived aryl radical could then undergo H-abstraction to produce alkyl radical 2.71 that could be oxidized by CuBr₂ present in the mixture in the manner previously described by Kochi to give CuIII-alkyl intermediate 2.72. First, a ligand transfer process could occur to give alkyl bromide 2.66 (oxidative substitution) or an inner-sphere electron transfer process could lead to alkyl cation 2.73 that could rapidly eliminate to form the desired olefin 2.66. After facilitating these processes, CuBr₂ would undergo net reduction to CuIBr that could feed in a new catalytic cycle by promoting the decomposition of 2.69.

Notably, when acetonitrile is replaced with CCl₄, the major product formed is alkyl chloride 2.74, isolated in a mixture with small amounts of alkyl bromide 2.66 and olefin 2.65 (Figure 2.9B). No aryl chloride is observed, indicating the short-lived nature of the aryl radical as well as the favorable intramolecular H-abstraction. Additionally, this result hints at a solvent effect in the reaction.
Figure 2.9 Investigations for the desaturation of a linear aliphatic alcohol. A. Proposed reaction mechanism. B. Outcome of the desaturation in a non-coordinating solvent.

A first attempt to suppress formation of bromide 2.66 was to screen other copper salts. However, as shown in Table 2.5, these experiments did not provide any useful data (Entries 2–4) while the use of other metal-based oxidants led to decomposition of the starting material (Entries 5–9). Given this data, the logical step forward was to continue using CuBr₂ and to find an additive or ligand to influence its reactivity and ultimately the reaction outcome.
Table 2.5 Screening other metal-based oxidants to avoid formation of bromide 2.66 \(^{a}\) Isolated yield, ratio determined upon integration of the \(^1\)H-NMR spectrum of the purified mixture.

| Entry | Oxidant       | Yield (%) \(^{a}\) (2.65 : 2.66) |
|-------|---------------|----------------------------------|
| 1     | CuBr\(_2\)    | 42 (3 : 1)                       |
| 2     | CuBr          | 24 (6.7 : 1)                     |
| 3     | CuBr(PPh\(_3\)) | < 5% of 2.65                   |
| 4     | CuF\(_2\)     | 14 (1 : 0)                       |
| 5     | Cu(OAc)\(_2\) | < 5% of 2.65                     |
| 6     | CoCl\(_2\) \(\cdot\) 6H\(_2\)O | decomp                           |
| 7     | Co(ClO\(_4\))\(_2\) \(\cdot\) 6H\(_2\)O | decomp                           |
| 8     | FeCl\(_3\)    | decomp                           |
| 9     | Pb(OAc)\(_4\) | decomp                           |
| 10    | \([\text{Cp}_2\text{Fe}]\)PF\(_6\) | decomp                           |

The screening of additives was structured around the proposed mechanism (Figure 2.9). Initially, ligands were tested to affect the oxidation potential of the metal and the ligand-transfer process (Table 2.6, Entries 2–4).\(^{21}\) It was found that the electron-donating phenanthroline (phen) decreased the olefin:bromide ratio (Entry 3) while the electron-withdrawing 2-acetyl-cyclohexanone\(^{28}\) did not affect the product ratio (Entry 4). Attempts were then made to promote \textit{in situ} base-mediated elimination of the alkyl bromide to the desired olefin (Entries 5–7), but these efforts were to no avail. Other single-electron oxidants were added to the mixture hoping for an increased olefin ratio, however these negatively affected the reaction (Entries 8–13). Then, the possibility of 2.66 forming as a result of radical recombination of a discrete alkyl radical 2.71 and a Br\(^+\), was investigated by screening common radical scavengers (Entries 14–17). To our surprise, TEMPO\(^{29}\) reduced the amount of 2.66 to an acceptable ratio (Entry 17) while no recombination products were detected. Based on literature precedent, it was then proposed that TEMPO might reduce CuBr\(_2\) to CuBr via a Cu-TEMPO complex, thus leading to a more efficient catalytic cycle.\(^{30}\)
Despite a positive step forward with the discovery of TEMPO, the transformation remained rather poor in terms of product yield. Given the extensive screening already performed, a more drastic change was to alter the structure of the directing group. The structure of the triazene moiety was modified and bases of different pKa values were used (Table 2.7). The goal was to affect the protonation of the triazene moiety by TFA and to ultimately improve the rate of aryl radical formation. It was thus empirically found that diethylamine leads to a better result (Entry 2) than the previously used pyrrolidine (Entry 1), so it was incorporated in the final structure of the “portable desaturase”.

Table 2.6 Additive screening to minimize formation of bromide 2.66

| Entry | Additive      | Yield (%) | (2.65 : 2.66)\(^a\) |
|-------|---------------|-----------|----------------------|
| 1     | PPh\(_3\)     | <5% of 2.65, complex mix |                     |
| 2     | phen          | 47 (1 : 1.5) |                      |
| 3     | 2-Ac-cyclohexanone | 52 (4 : 1)         |                      |
| 4     | DMAP          | 40 (5 : 1)    |                      |
| 5     | AgTFA         | decrop       |                      |
| 6     | Na\(_2\)TFA   | 40 (3 : 1)    |                      |
| 7     | CAN           | <5% of 2.65, complex mix |         |
| 8     | PIFA          | decrop       |                      |
| 9     | Selectfluor   | decrop       |                      |
| 10    | (NH\(_4\))(\(_2\)S\(_2\)O\(_8\)) | decrop       |                      |
| 11    | Ce(OTf)\(_3\) | decrop       |                      |
| 12    | Ce(SO\(_4\))\(_2\) | complex mixture |         |
| 13    | hydroquinone  | NA (4 : 1)\(^b\) |                      |
| 14    | BHT           | 34 (4 : 1)    |                      |
| 15    | 4-OH-TEMPO    | 38 (4.5 : 1)  |                      |
| 16    | 4-OH-TEMPO    | 24 (3 : 1)    |                      |
| 17    | TEMPO         | 36 (10 : 1)   |                      |

\(^{a}\) Isolated yield, ratio determined upon integration of the \(^1\)H-NMR spectrum of the purified mixture. \(^{b}\) Ratio determined by integration in the \(^1\)H-NMR of the crude mixture after work-up (no purification).
Table 2.7 Testing various amines towards a final structure of the “portable desaturase”. Isolated yield, ratio determined upon integration of the \(^1\)H-NMR spectrum of the purified mixture.

The electronic effect of substituents on the aryl ring towards the reactivity of the aryl radical\(^3\) was then investigated (Figure 2.10A). It was found that a tosyl triazene derivative (Entry 2) gave the best results, while both para-methoxy (Entry 3) and para-fluoro (Entry 4) substituents disrupted the reactivity in this reaction. As a result, a final “portable desaturase” was developed and applied successfully on 2.79 to obtain a 47% yield of a 10:1 mixture of olefin 2.80 and alkyl bromide 2.81.
Figure 2.10 Final investigations into the structure of the “portable desaturase” A. Testing the effects of aryl substituents on the outcome of the desaturation reaction. B. Final structure of the “portable desaturase”.

Having identified an additive (TEMPO) to improve product distribution in the desaturation of simple secondary alcohols (e.g. 2.64), as well as an optimized directing group for more efficient H-abstraction (Table 2.6, Entry 17 vs. Figure 2.10B), we sought to investigate the generality of this method. Thus, cyclopentyl ethanol derivative 2.82 was next employed as substrate. After a few optimization trials, it was found that in order to minimize formation of Sandmeyer product 2.85, the CuBr₂ loading could be lowered to 5 mol% (Entry 1). Furthermore, since CH₃CN appeared to strongly promote reduction of the triazene to 2.84 (Entry 1), CH₃NO₂ was employed as solvent to improve the ratio of alkene 2.83 (Entry 2). Given that no alkyl bromide ever resulted from either 2.60 or 2.82, initially the benefit of using TEMPO as an additive was a minimal improvement in the reaction yield (Entry 3). However, the role of TEMPO became clear after a series of control experiments were executed (Entries 5–7). To our surprise, it was discovered that TEMPO alone could facilitate
the desaturation of 2.82 in slightly better yield with the obvious elimination of Sandmeyer byproduct 2.85 (Entry 5). When the reaction was run only with acid (Entry 6), without a copper oxidant or TEMPO, trace amounts of the desired product were observed, accompanied by mostly nonspecific decomposition. When the acid was left out, no reaction took place and the starting material was recovered intact (Entry 7).

Table 2.8 Final optimization studies and development of final desaturation conditions. Conditions: reactions run on 0.025 mmol of 2.86 in CH₃NO₂; “yields and ratios are based on ¹H-NMR integration relative to an internal standard (1,3,5-trimethoxybenzene); †reaction run in CH₂CN (0.025 M); ‡isolated yield; †reaction run at 0.05 M.

These exciting metal-free desaturation conditions prompted a final stage of optimization of the reaction with respect to acid, temperature, concentration and nitroxide radical. Using three equivalents of TFA as the acid, the temperature can be lowered to 60 °C and the reaction time shortened to 1.5 hours to give the desired olefin 2.83 and along with minor amounts of 2.84 in 68% isolated yield (Entry 7). When the stronger triflic acid (2 equiv) was employed, the reaction proceeded efficiently at room temperature over 3 hours to
give 2.83 in 54% yield (Entry 10). Interestingly, the weaker H₃PO₄ returned the starting material, while TsOH gave more of 2.84 (Entries 8, 9). Increasing the reaction concentration to 0.05 M reduced the yield to 45% (Entry 10). Finally, other nitroxide radical species were tested with the hope to increase the reaction efficiency, but both the less hindered AZADO and the more hindered adamantyl nitroxide were inferior to the cheaper, commercially available TEMPO (Entries 11, 12). Thus, with two sets of conditions in hand (Entries 7 and 10), the substrate scope of the newly developed desaturation reaction system was explored.

2.4 References

(1) Chen, K.; Baran, P. S. Nature 2009, 459, 824.
(2) Ishihara, Y.; Baran, P. S. Synlett 2010, 1733.
(3) Chen, K.; Richter, J. M.; Baran, P. S. J. Am. Chem. Soc. 2008, 130, 7247.
(4) a) Breslow, R.; Snider, B. B.; Corcoran, R. J. J. Am. Chem. Soc. 1974, 96, 6792; b) Johnson, J. A.; Li, N.; Sames, D. J. Am. Chem. Soc. 2002, 124, 6900; c) Gong, H.; Williams, J. R. Org. Lett. 2006, 8, 2253; d) Jung, M. E.; Johnson, T. W. J. Am. Chem. Soc. 1997, 119, 12412; e) Yoshimitsu, T.; Sasaki, S.; Arano, Y.; Nagaoka, H. J. Org. Chem. 2004, 69, 9262.
(5) a) Kochi, J. K.; Subramanian, R. V. J. Am. Chem. Soc. 1965, 87, 4855; b) Kochi, J. K.; Bacha, J. D. J. Org. Chem. 1968, 33, 2746; c) Jenkins, C. L.; Kochi, J. K. J. Am. Chem. Soc. 1972, 94, 843.
(6) Mackiewicz, P.; Furstost, R. Tetrahedron 1978, 34, 3241.
(7) Galli, C. Chem. Rev. 1988, 88, 765.
(8) Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. J. Am. Chem. Soc. 1977, 99, 7589.
(9) Lewin, A. H.; Dinwoodie, A. H.; Cohen, T. Tetrahedron 1966, 22, 1527.
(10) Han, G. H.; McIntosh, M. C.; Weinreb, S. M. Tetrahedron Lett. 1994, 35, 5813.
(11) Denenmark, D.; Winkler, T.; Waldner, A.; De Mesmaeker, A. Tetrahedron Lett. 1992, 33, 3613.
(12) Bridger, R. F.; Russell, G. A. J. Am. Chem. Soc. 1963, 85, 3754.
(13) Kimball, D. B.; Haley, M. M. Angew. Chem. Int. Ed. 2002, 41, 3338.
(14) a) Satyamurthy, N.; Barrio, J. R.; Schmidt, D. G.; Kammerer, C.; Bida, G. T.; Phelps, M. E. J. Org. Chem. 1990, 55, 4560; b) Patrick, T. B.; Juehne, T.; Reeb, E.; Hennessy, D. Tetrahedron Lett. 2001, 42, 3553; c) Patrick, T. B.; Willaredt, R. P.; DeGonia, D. J. J. Org. Chem. 1985, 50, 2232.
(15) Gross, M. L.; Blank, D. H.; Welch, W. M. J. Org. Chem. 1993, 58, 2104.
(16) Bräse, S. Acc. Chem. Res. 2004, 37, 805.
(17) a) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T. Y.; Li, H.; Bräse, S.; Ramanjulu, J. M. J. Am. Chem. Soc. 1997, 119, 3421; b) Ready, J. M.; Reisman, S.
E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1270.

(18) a) Doyle, M. P.; Siegfried, B.; Elliott, R. C.; Dellaria, J. F. *J. Org. Chem.* **1977**, *42*, 2431; b) Dickerman, S. C.; DeSouza, D. J.; Jacobson, N. *J. Org. Chem.* **1969**, *34*, 710.

(19) Pines, S. H.; Purick, R. M.; Reamer, R. A.; Gal, G. *J. Org. Chem.* **1978**, *43*, 1337.

(20) Cohen, T.; Lewarchik, R. J.; Tarino, J. Z. *J. Am. Chem. Soc.* **1974**, *96*, 7753.

(21) Kochi, J. K.; Bemis, A.; Jenkins, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 4616.

(22) a) Kochi, J. K. *J. Am. Chem. Soc.* **1955**, *77*, 5090; b) Kochi, J. K.; Subramanian, R. V. *J. Am. Chem. Soc.* **1965**, *87*, 1508.

(23) Kochi, J. K. *J. Am. Chem. Soc.* **1955**, *77*, 5274.

(24) Zollinger, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 141.

(25) Barrio, J. R.; Satyamurthy, N.; Ku, H.; Phelps, M. E. *J. Chem. Soc., Chem. Commun.* **1983**, *443*.

(26) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 856.

(27) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351.

(28) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(29) Vogler, T.; Studer, A. *Synthesis* **2008**, *2008*, 1979.

(30) Michel, C.; Belanzoni, P.; Gamez, P.; Reedijk, J.; Baerends, E. J. *Inorg. Chem.* **2009**, *48*, 11909.

(31) a) Pryor, W. A.; Echols, J. T.; Smith, K. *J. Am. Chem. Soc.* **1966**, *88*, 1189; b) Takayama, K.; Kosugi, M.; Migita, T. *Chem. Lett.* **1973**, *193*; c) Migita, T.; Takayama, K.; Abe, Y.; Kosugi, M. *J. Chem. Soc., Perkin Trans. 2* **1979**, *1137*.

(32) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

(33) Debuigne, A.; Chan-Seng, D.; Li, L.; Hamer, G. K.; Georges, M. K. *Macromolecules* **2007**, *40*, 6224.
3. Applications
3.1 Applications of the Desaturation Reaction on Simple Aliphatics

The new “portable desaturase” triazene sulfonyl chloride (\( o \)-Tosyl Triazene Chloride, Tz’\( \text{Cl} \), 3.3) was prepared in two simple, scalable steps (Figure 3.1) in 60% overall yield. Further, the installation of Tz’\( \text{Cl} \) on a variety of aliphatic alcohols and amines proceeded smoothly under mild conditions to give the desired products in yields within the 73–95% range (see Section 5. Experimental for data). The scope of the desaturation was next investigated on both simple and complex aliphatics.

![Figure 3.7 Synthesis of the “portable desaturase”, Tz’\( \text{Cl} \)](image)

As shown in Figure 3.2, a variety of primary and secondary alcohols are viable substrates for the guided dehydrogenation reaction, giving moderate to good yields of olefinic products. In these systems, the desaturation reaction takes place most efficiently when a tertiary carbon center is in a 1,3 relationship to the functionality carrying the portable desaturase and this selectivity implies a 1,7 H-abstraction\(^1\) by the intermediate aryl radical. Such a process has been only briefly described in the literature, with aryl radicals usually preferring the 1,5 or 1,6 H-abstraction mode of reactivity.\(^2\)
When simple aliphatic secondary alcohols were employed in the guided desaturation (2.80, 3.4–3.6), good selectivity for tertiary alkyl positions was detected and desired alkenes were obtained as the only isolable products in moderate yields. For these substrates, the reaction proceeded best when TFA was used as acid, whereas TfOH generally led to decomposition. On a substrate designed to test for oxidation at a tertiary alkyl site versus a benzylic site, the desaturation reaction provided the olefin product 3.4 (36% yield) and no styrene derivatives were observed. This data does not rule out the possibility of H-abstraction at the benzylic position, but such potential products may be unstable under the reaction conditions (vide infra for discussion and Figure 3.2B). Furthermore, because the portable desaturase favors H-abstraction at proximal tertiary alkyl positions, site-selective oxidation can be performed (e.g. 3.5) and functional groups such as olefins are also tolerated in the
reaction (e.g. 3.6). An excellent substrate for the guided desaturation is menthol, which cleanly gives isopulegol tosylate 3.10 in 92% yield in an efficient desaturation process that might be accommodated by the more rigid molecular organization of the substrate.

*Aliphatic primary alcohols* are also suitable substrates for the guided desaturation reaction. Alkenol tosylates 3.7 and 3.8 were obtained in good yield as mixtures of olefin isomers due to uncontrolled elimination from the corresponding tertiary alkyl cations. Cyclic substrates behave well under the desaturation conditions, giving products such as 2.83 and 3.9 in good yields (68% and 51% respectively). These substrates reiterate a limitation of the method, the formation of small amounts of reduction product (e.g. 2.84) that are difficult to separate from the desired alkene.

Notably, when applied to alcohol-derived substrates, the desaturation reaction provided only homoallylic tosylates and no other byproducts were observed. However, given the modest yields obtained in certain cases (e.g. 2.80, 3.4–3.6), it is likely that allylic tosylates are being generated (by elimination of the alkyl cation towards the tosylate group) even if they could never be detected or isolated. Indeed, such a mode of elimination is operative when allylic tosylamine 3.12b is formed from 3.17, the nitrogen analog of 2.79 (Figure 3.2A). However, in the case of alcohol-derived substrates, the resulting allylic tosylates (e.g. 3.18, 3.20, 3.23, 3.26, Figure 3.2) are predicted to be prone to rapid decomposition via a π-allyl carbocation intermediate (Figure 3.3A) while generating TsOH. As a consequence, substrates leading to allylic tosylates (e.g. alcohols in a 1,2 relationship to a tertiary center) are not well suited for this method (Figure 3.3C).
Figure 8.3 Discussing the problems with the linear substrates. A. Proposed decomposition route of allylic tosylates presumed to be forming in situ. B. Limitation of the desaturation at benzylic sites. C. Proposed experiment to test for the possibility of 1,2 H-abstraction. Conditions: Substrate (0.100 mmol), TEMPO (1 equiv), TFA (3 equiv), CH$_3$NO$_2$ (0.025 M), 60 °C, 1.5 h (isolated yield).

In addition to primary and secondary alcohols, *aliphatic amines* are also competent substrates for the guided desaturation reaction, leading to either homoallylic (3.11, 3.13, 3.14, Figure 3.2) or allylic tosylamines (3.15 and 3.16, Figure 3.2). It was found that for amine-derived substrates, TfOH performs slightly better in the desaturation reaction compared to TFA. Indeed, menthylamine behaves well to give 3.11 in 59% yield, while 3.12...
is obtained in 60% yield as a 10:1 mixture of homoallylic (major) and allylic (minor) tosylamines. Furthermore, allylic tosylamines such as 3.16 can be prepared selectively in good yield (50%) and amino esters are selectively desaturated to provide valuable dehydroaminoesters (3.13–3.15) in useful yields.

3.2 Applications of the Desaturation Reaction in Complex Settings

With the goal of exploring this methodology in more complex settings, a series of natural product derived substrates were synthesized and tested under the reaction conditions. As such, dihydrojunosinol derivative 3.27 was identified as a desirable substrate for the desaturation reaction. Although similar in substructure with the simpler menthol, 3.27 contains two equidistant, but sterically different tertiary sites available for oxidation. Using Procedure A, the desaturation reaction generated a 2:1 mixture of inseparable regioisomers in 46% yield (Figure 3.4A). This result suggests that H-abstraction with an aryl radical is indifferent to the steric environment around the C–H bond as long as a favorable geometry for abstraction is possible.3

Dehydroabietyl amine derivative 3.29 poses an interesting challenge for selective C–H functionalization, given two reactive benzylic sites, a hindered tertiary ring junction and an otherwise unfunctionalized decalin system. Treatment of 3.29 with TEMPO (1 equiv) in the presence of TfOH (2 equiv) at a temperature as low as 4 °C gave two oxidation products (Figure 3.4B). The major product was the rearranged and cyclized sulfonamide 3.30 (30% yield), which arises by an interrupted desaturation process. It appears that upon formation of the tertiary carbocation, a Wagner–Meerwein rearrangement occurs to provide the more stabilized benzylic cation, which is then trapped intramolecularly by the tosylamine moiety. The minor product 3.31 (16% yield) can be accounted for by initial abstraction from an
unactivated methylene C–H bond and subsequent termination to the disubstituted olefin. Thus, the guided desaturation affords oxidation products at sites other than the more reactive benzylic positions that would be targeted in intermolecular oxidation processes.

![Figure 3.9 Applications of the guided desaturation reaction on complex substrates. A. Desaturation of a sesquiterpene derivative to a mixture of alkene regioisomers. B. Example of an interrupted desaturation reaction and methylene dehydrogenation. C. Application of the desaturation reaction towards diene synthesis in a complex setting. D. Synthesis of a tetrapeptide incorporating a dehydroleucine amino-acid residue. *Yield based on a mixture of product and reduction byproduct (10:1), see Section 5. Experimental.](image-url)

To demonstrate the ability to generate dienes in complex settings, triterpene derivative 3.32 containing a trisubstituted olefin and a free secondary alcohol was subjected to the reaction conditions (Figure 3.4C). As a result, 3.33 was obtained in 47% yield as the
major product of the reaction after allylic 1,8 H-abstraction, oxidation and elimination to the most stable diene system. It is of note that the secondary alcohol remains untouched under these conditions and the sensitive diene functionality is safely contained in the final product.\(^4\)

Following the successful desaturation of aminoesters (3.13–3.15, Figure 3.2), this protocol was further tested on a more complex tetrapeptide. When 3.34 was subjected to the reaction conditions, the desaturated product 3.35 was isolated in 35% yield without racemization of any of the four chiral centers (Figure 3.4D). Additionally, the portable desaturase allows for site-selective oxidation on substrates such as 3.34 that are distinguished by strong chelating ability, multiple sites available for oxidation and reactive functional groups.

Although successful in numerous cases, the desaturation reaction described herein does present substrate limitations (Figure 3.4). Although no obvious patterns arose, factors such as a sterically hindered tertiary site (e.g. 3.38, 3.46, 3.47, 3.58 or 3.54), labile or reactive functional groups (e.g. 3.39, 3.49, 3.51, 3.52, 3.56 or 3.59) and geometrical constraints (e.g. 3.45, 3.48 or 3.58) generally led to very poor product yields or nonproductive decomposition.
Figure 3.10 Substrates which were unproductive during the desaturation reaction. *Low product yields detected by $^1$H-NMR (<20% yield). Conditions: 5 mol% CuBr$_2$, TEMPO (1 equiv), CH$_3$NO$_2$, 80 ºC, 3h (see Section 2. Reaction development for details).

In addition to substrate limitations due to decomposition under the reaction conditions, another limitation of the method was the introducing the directing group (Tz$^\circ$Cl) onto highly hindered alcohols (Figure 3.5, 3.61–3.65). Additionally when benzylic alcohols 3.68 and 3.69 were utilized, no product was isolated probably to the in situ decomposition of the tosylate-like products. Indeed, when treated with Tz$^\circ$Cl under basic conditions, sclareolide-derived diol 3.66 undergoes ring closing by displacement of the OTz$^\circ$ functionality by the electron rich tertiary alcohol to give ambroxide 3.67 (Figure 3.5).
3.3 References

(1) See ref 10 (Section 1) and ref 11 (Section 2)
(2) See refs 8, 9 (Section 2)
(3) a) Huang, X. L.; Dannenberg, J. J. *J. Org. Chem.* 1991, 56, 5421; b) Cohen, T.; Smith, K. W.; Swerdloff, M. D. *J. Am. Chem. Soc.* 1971, 93, 4303; c) Citterio, A.; Minisci, F.; Vismara, E. *J. Org. Chem.* 1982, 47, 81.
(4) Stang, E. M.; White, M. C. *J. Am. Chem. Soc.* 2011, 133, 14892.
4. Mechanistic Investigations
4.1 Mechanistic Studies

Preliminary experiments to clarify both the mechanism of the reaction and the role of TEMPO are discussed below. The first goal was to confirm the 1,7 H-abstraction event that productively leads to the olefin product through deuterium labeling (Figure 4.1). Thus, when deuterium was incorporated at the tertiary alkyl site in 4.1 (Figure 4.1, eq 1), deuterium transfer was indeed observed in the desaturated product 4.2, but the reaction is less efficient (34% yield for 4.2, vs. 68% for 2.83, see Figure 3.2) and a new minor product was observed that is tentatively assigned to the olefin isomer 4.3. Presumably the stronger deuterium–carbon bond diverts the aryl radical towards the normally less reactive methylene C–H bond. Additionally, when deuterium was incorporated at the α and β positions, no D-transfer occurred and the expected olefins 4.5 and 4.7 were isolated in good yields.

**Figure 4.11 Experiments to support the proposed 1,7 H-abstraction process.** aConditions: Substrate (0.100 mmol), TEMPO (1 equiv), TFA (3 equiv), CH$_3$NO$_2$ (0.025 M), 60 °C, 1.5 h. bYields are based on $^1$H-NMR integration relative to an internal standard (1,3,5-trimethoxybenzene);
produce a reactive vinyl radical \(4.9\), which performs a favorable 1,5 H-abstraction to generate tertiary alkyl radical \(4.10\) that is further oxidized and terminated to an olefin.

![Figure 4.12 In situ trapping of the aryl radical](image)

Thirdly, in order to clarify the role of TEMPO in the reaction, aniline substrate \(4.12\) was prepared and converted into the corresponding diazonium salt, a presumed intermediate in the reaction (Figure 4.3A). When TEMPO (1 equiv) was added at room temperature, the dehydrogenation event took place and olefin \(2.61\) was isolated in 44% yield (Entry 1). When the TEMPO loading was lowered to 0.1 equiv (Entry 2), the reaction provided the product in only a slightly lower yield (31%, TON = 3); meanwhile, the absence of TEMPO led to nonspecific decomposition of the starting material (Entry 3). This data indicates that TEMPO can support a catalytic cycle, but is inefficient under the current reaction conditions. Importantly, these transformations proceed under *acid-free* conditions, implying that TFA is not required in the oxidation events, but merely to liberate the diazonium salt from the starting triazene.
Mechanistic investigations and proposed reaction mechanism. 

A. Example of a desaturation reaction starting from an aniline derivative. 
B. Initial result supporting a catalytic cycle in TEMPO. 
C. Proposed sequence of events for the guided desaturation reaction. 

- Yields are based on $^1$H-NMR integration relative to an internal standard (1,3,5-trimethoxybenzene).
- The reaction resulted in mostly nonspecific decomposition.
- Isolated yield.

### 4.2 Proposal for the Reaction Mechanism

Based on our experimental results and literature precedent, the proposed reaction mechanism for the TEMPO-mediated desaturation reaction is presented in Figure 4.3C. First, TFA converts triazene 2.82 into the diazonium TFA salt 4.14. TEMPO then promotes its reductive decomposition to aryl radical 4.15, an event concomitant with the generation of $N_2$ and the oxidation of TEMPO to TEMPO$^+$. Once formed, 4.15 undergoes H-abstraction to generate an alkyl radical intermediate 4.16 which is oxidized to the corresponding carbocation 4.17 by TEMPO$^+$ previously formed in the reaction. Spontaneous elimination from 4.17 leads to the olefin product 2.83, with TEMPO acting as a single-electron shuttle in the overall process. Remarkably, no aryl or alkyl-TEMPO recombination adducts are observed. Finally, based on the proposed mechanism, the reaction should be catalytic in TEMPO and preliminary results show that this is true (Figure 4.3A, TON = 3; Figure 4.3B,
TON = 2), but suffers from low efficiency. Further experiments are needed to fully explore this possibility.

4.3 References

(1) Beckwith, A. L. J.; Meijs, G. F. *J. Chem. Soc., Chem. Commun.* **1981**, *595*.
(2) Zhang, F.; Liu, Y. C. *Chin. Sci. Bull.* **2010**, *55*, 2760.
Conclusion and Distribution of Credit

A new chemical moiety, Tz\(^2\)Cl (3.3), has been designed to mimic processes observed in Nature, leading to desaturated aliphatics. The chemistry performed by this directing group is centered on the high reactivity of an aryl radical masked as an aryl triazene. This application expands the chemistry of the aryl radical, as it exploits this reactive intermediate as a useful tool for C–H functionalization. The desaturation reaction described herein is applicable on simple substrates derived from saturated alcohols and amines, giving olefin products in a predictable fashion without any overoxidation. Some of the drawbacks of this method are the modest product yields, the formation of minor amounts of inseparable reduction products and the occasional difficulties in purification. Nonetheless, the guided desaturation reaction can be successfully applied in complex settings, as it shows very good functional group tolerance while leading to useful oxidized products. Additionally, the intriguing reaction mechanism suggests that TEMPO can act as a single-electron shuttle, providing impetus to further investigate a truly catalytic version of this transformation. Studies to expand the scope of this transformation and apply it in two-phase terpene total synthesis are continuing in our laboratory.

The results presented in this document have been obtained by myself with the following exceptions: the data presented in Table 2.8 was gathered in collaboration with Will Gutekunst and Dr. Abraham Mendoza; the synthesis of Tz\(^2\)Cl presented in Figure 3.1 was designed by myself but it was scaled up (>100 g) with help from Will Gutekunst; the substrates presented in Figure 3.2 were identified by myself, but the data for 2.80, 3.4–3.6, 3.11, 3.12, 3.16 was collected by Will Gutekunst, while Dr. Abraham Mendoza ran the
experiments for $3.13-3.15$; the proposal presented in Figure 2.3 was devised in collaboration with Will Gutekunst and Dr. Abraham Mendoza; the results presented in Figure 3.3A, C were gathered by myself and double-checked by Will Gutekunst while Dr. Abraham Mendoza obtained the yield on $3.29$, synthesized $3.34$ and obtained the yield for $3.35$ (Figure 3.3B, D); the experiment presented in Figure 4.2 was executed by Dr. Abraham Mendoza following a lead identified by myself in the early stages of the project; Will Gutekunst obtained the data presented in Figure 4.3B, while the mechanism proposal described in Figure 4.3C was a team collaboration with Will Gutekunst and Dr. Abraham Mendoza. Jorge Otero helped with synthesizing starting materials.
5. Experimental
**General procedures:** All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), acetonitrile (CH₃CN), methanol (MeOH) and triethylamine (Et₃N) were obtained by passing these previously degassed solvents through activated alumina columns. Dry nitromethane (CH₃NO₂) was obtained by distillation from CaH₂ and stored under Ar over 4Å MS. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO₄), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (pTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl₃ @ 7.26 ppm ¹H NMR, 77.16 ppm ¹³C NMR; DMSO-d₆ @ 2.50, 3.30 ppm ¹H NMR, 39.51 ppm ¹³C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time of flight reflectron experiments. IR spectra were recorded on a
Perkin Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

**General procedure for the synthesis of bromo-aryl triazenes (GP1)**

\[
\begin{align*}
\text{Br} & \text{NH}_2 \quad \text{NaNO}_2 (1.5 \text{ equiv}), \text{conc HCl, 0 } ^\circ \text{C, 10 min}\nonumber \\
& \text{then Et}_2\text{NH (1.1 equiv), aq. KOH (1M), 0 } ^\circ \text{C, 30 min} \nonumber \\
& \rightarrow \text{Br} \quad \text{N}_2\text{N}^-\text{NEt}_2 
\end{align*}
\]

**Compound 3.2**\(^1\): A 250 mL round bottom flask equipped with a stir bar was charged with 5-methyl-2-bromoaniline 3.1 (15 g, 80.620 mmol, 1 equiv) which was suspended in conc. HCl (81 ml) to obtain a white slurry. This mixture was cooled at 0 °C before a solution of NaNO\(_2\) (8.34 g, 120.930 mmol, 1.5 equiv) in H\(_2\)O (10.4 mL) was added dropwise (Caution! Toxic gases form during this addition). The resulting yellow solution was stirred at 0 °C for 10 min after which a solution of diethylamine (6.5 g, 88.680 mmol, 1.1 equiv) in 1 M KOH (68.2 mL) was poured into the reaction flask. The reaction was allowed to proceed at 0 °C for 1h before it was quenched with 3 M NaOH (or KOH) until the pH reached 12. The product was extracted with EtOAc (3 x 75 mL). The combined organic layers were then washed with brine, dried over MgSO\(_4\), filtered and concentrated in vacuo. The desired product 3.2 (19.68 g, 91% yield) was isolated after rapid chromatography (silica gel, 49:1 hexanes/EtOAc) as a brown oil.

**Physical state**: brown oil;

\[R_f = 0.72 \ (4:1 \ \text{hexanes/EtOAc});\]

\(^1\) Procedure adapted from: Gross, M. L.; Blank, D. H.; Welch, W. M. *J. Org. Chem.* 1993, 58, 2104.
HRMS (m/z): calcd for C_{11}H_{16}BrN_{3}H^+, [M+H]^+, 270.0600; found, 270.0606;

IR (film) ν_{max} = 2973, 2933, 1465, 1409, 1385, 1341, 1249, 1105, 1032, 802;

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.43 (d, $J = 8.1$ Hz, 1 H), 7.19 (s, 1 H), 6.80 (d, $J = 7.9$ Hz, 1 H), 3.79 (q, $J = 7.0$ Hz, 4 H), 2.30 (s, 3 H), 1.31 (s, 6 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 148.3, 137.8, 132.7, 127.1, 119.2, 116.6, 49.2, 41.9, 21.2, 14.6, 11.0.

**Compound 5.1**: Prepared from 2-bromoaniline (495 mg, 2.9 mmol, 1 equiv) following the GP1. The product was isolated in 100% yield (732.6 mg) and it was used in the subsequent reaction without further purification. The analytical data was identical to the original report.

**Compound 5.2**: Prepared from 2-bromo-4-fluoroaniline (573.8 mg, 3.02 mmol, 1 equiv) following the GP1. The product was isolated in 84% yield (736.9 mg) after column chromatography (silica gel, 20:1 hexanes/Et$_2$O).

**Physical state**: brown oil;

$R_f = 0.66$ (4:1 hexanes/EtOAc);

HRMS (m/z): calcd for C$_{10}$H$_{11}$BrFN$_3$H$^+$ [M+H]$^+$, 272.0192; found, 272.0193;

IR (film) ν$_{max}$ = 2973, 2871, 1593, 1476, 1419, 1341, 1249, 1180, 1032;

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.70(ddd, $J = 13.1$, 8.6, 3.9 Hz, 2 H), 7.31 (ddd, $J = 9.1$, 7.6, 2.9 Hz, 1 H), 3.99 (t, $J = 6.2$ Hz, 2 H), 3.85 (t, $J = 6.3$ Hz, 2 H), 2.17 – 2.01 (m, 4 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 159.0, 157.4, 145.8, 145.8, 136.7, 136.7, 123.3, 123.1,
Compound 5.3: Prepared from 2-bromo-4-methoxyaniline (1.047 mg, 5.21 mmol, 1 equiv) following the GP1. The product was isolated in 88% yield (1.292 g) and it was used in the subsequent reaction without further purification.

Physical state: orange solid;

$R_f = 0.4$ (4:1 hexanes/EtOAc);

m.p. = 50–52 °C;

HRMS (m/z): calcd for C$_{11}$H$_{14}$BrN$_3$OH$^+$ [M+H]$^+$, 284.0393; found, 284.0396;

IR (film) $\nu_{\text{max}} = 2969, 1741, 1596, 1483, 1421, 1338, 1212, 1032$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.35 (d, $J = 8.9$ Hz, 1 H), 7.13 (s, 1 H), 6.82 (d, $J = 8.9$ Hz, 1 H), 4.01 – 3.58 (m, 7 H), 2.03 (s, 4 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 158.3, 143.4, 120.5, 119.7, 118.2, 115.2, 56.5, 24.6.

Compound 5.4: Prepared from 2-bromoaniline (500 mg, 2.9 mmol, 1 equiv) following the GP1. The product was isolated in 98% yield (765.5 mg) and it was used in the subsequent reaction without further purification.

Physical state: brown oil;

$R_f = 0.41$ (4:1 hexanes/EtOAc);

HRMS (m/z): calcd for C$_{10}$H$_{12}$BrN$_3$OH$^+$ [M+H]$^+$, 270.0236; found, 270.0238;

IR (film) $\nu_{\text{max}} = 2968, 2856, 1465, 1421, 1349, 1164, 1106, 1014, 754$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.60 (dd, $J = 8.0, 1.3$ Hz, 1 H), 7.42 (dd, $J = 8.0, 1.6$ Hz, 1 H), 7.29 – 7.23 (m, 1 H), 7.09 – 7.02 (m, 1 H), 3.87 (s, 8 H);
$^{13}$C NMR (151 MHz, CDCl$_3$) δ 147.6, 133.3, 127.9, 127.4, 120.4, 118.7, 77.3, 77.1, 76.9, 66.4.

**General procedure for the synthesis of triazene sulfonyl chlorides (GP2)**

**Compound 3.3**: A 2 L round bottom flask equipped with a stir bar and a septum, previously flame-dried under vacuum, was charged with 3.2 (31.4 g, 116.66 mmol, 1 equiv), azeotroped from benzene (100 mL) and kept under Ar. After addition of Et$_2$O (1 L), the solution was cooled at –78 °C and sec-BuLi (1.4 M in cyclohexane, 140.000 mmol, 100 mL, 1.2 equiv) was added dropwise to give a red solution which was stirred for 30 min at the same temperature. After this time, SO$_2$(g) was condensed via cannula into the reaction flask until the mixture became a pale yellow suspension (and the color is persistent; 5–10 min). The resulting mixture was stirred for 1 h at –78 °C, then at room temperature for 5 h before the solvent was removed *in vacuo* to give a pale brown solid which was maintained under an atmosphere of Ar. The resulting solid (aryl sulfonate lithium salt) was dissolved in CH$_2$Cl$_2$ (1 L) and the solution was cooled at 0 °C before NCS (18.7 g, 140.000 mmol, 1.2 equiv) was added in one portion. The brown mixture was stirred at 0 °C for 10h/overnight before being quenched with a saturated solution of NH$_4$Cl (200 mL). The aqueous layer was extracted with EtOAc (3 x 200 mL) and the resulting organic solution was washed with brine (500
mL), dried over MgSO$_4$ and concentrated in vacuo. Thus Tz$^2$Cl 3.3 (23.26 g) was isolated after column chromatography (silica gel, 9:1 hexane/EtOAc) (69% yield).

**Physical state**: orange solid;

$R_f = 0.66$ (4:1 hexanes/EtOAc);

m.p. = 74–76 °C;

**HRMS ($m/z$)**: calcd for C$_{11}$H$_{16}$ClN$_3$O$_2$SH$^+$ [M+H]$^+$, 290.0724; found, 290.0727;

**IR (film) $\nu_{\max}$**: 2976, 2936, 1589, 1566, 1464, 1387, 1340, 1325, 1269, 1168, 1111;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.88 (d, $J = 8.3$ Hz, 1 H), 7.48 (s, 1 H), 7.00 (d, $J = 8.2$ Hz, 1 H), 3.94 – 3.83 (m, 4 H), 2.42 (s, 3 H), 1.39 (t, $J = 7.2$ Hz, 3 H), 1.30 (t, $J = 7.1$ Hz, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 148.8, 147.1, 134.1, 128.9, 124.8, 118.4, 49.8, 43.0, 22.0, 14.6, 11.5.

**Compound 2.59**: Prepared from 5.1 (732.6 mg, 2.89 mmol, 1 equiv) following the GP2. The product was isolated in 69% yield (547.8 mg) after column chromatography (silica gel, 10:1 hexanes/EtOAc).

**Physical state**: orange solid;

$R_f = 0.53$ (4:1 hexanes/EtOAc);

m.p. = 76–78 °C;

**HRMS ($m/z$)**: calcd for C$_{10}$H$_{12}$ClN$_3$O$_2$SH$^+$ [M+H]$^+$, 274.0411; found, 274.0413;

**IR (film) $\nu_{\max}$**: 2975, 2876, 1583, 1565, 1466, 1393, 1360, 1341, 1311, 1270, 1173, 1154, 1122;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.99 (d, $J = 8.1$ Hz, 1 H), 7.69 (d, $J = 8.2$ Hz, 1 H), 7.59 (dd, $J = 11.2$, 4.2 Hz, 1 H), 7.19 (t, $J = 7.7$ Hz, 1 H), 4.03 – 3.97 (m, 2 H), 3.91 – 3.84 (m, 2 H),
2.13 – 2.04 (m, 4 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 149.1, 136.5, 135.8, 128.9, 123.9, 118.1, 51.5, 48.0, 24.1, 23.4.

**Compound 5.5:** Prepared from 5.2 (1.17 g, 4.31 mmol, 1 equiv) following the GP2. The product was isolated in 69% yield (863.9 mg) after column chromatography (silica gel, 10:1 hexanes/EtOAc).

**Physical state:** orange solid;

$R_f$ = 0.43 (4:1 hexanes/EtOAc);

m.p. = 72–74 ºC;

**HRMS (m/z):** calcd for C$_{10}$H$_{11}$ClFN$_3$O$_2$SH$^+$ [M+H]$^+$, 292.0317; found, 292.0313;

**IR (film) $\nu_{max}$:** 2977, 2878, 1482, 1393, 1366, 1170;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (ddd, $J$ = 13.1, 8.6, 3.9 Hz, 2 H), 7.31 (ddd, $J$ = 9.1, 7.6, 2.9 Hz, 1 H), 3.99 (t, $J$ = 6.2 Hz, 2 H), 3.85 (t, $J$ = 6.3 Hz, 2 H), 2.14 – 2.03 (m, 4 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 159.0, 157.4, 145.8 (d, $J$ = 3.2 Hz), 136.7 (d, $J$ = 7.4 Hz), 123.3, 123.1, 119.7 (d, $J$ = 7.2 Hz), 115.6, 115.4, 51.5, 47.9, 24.1, 23.4.

**Compound 5.6:** Prepared from 5.3 (944.6 mg, 3.34 mmol, 1 equiv) following the GP2. The product was isolated in 66% yield (671.5 mg) after column chromatography (silica gel, 10:1 hexanes/EtOAc).

**Physical state:** yellow solid;

$R_f$ = 0.38 (4:1 hexanes/EtOAc);

m.p. = 94–96 ºC;
HRMS (m/z): calcd for C₁₁H₁₄ClN₃O₃SH⁺ [M+H]⁺, 304.0517; found, 304.0515;

IR (film) ν_max = 2973, 1602, 1486, 1360, 1268, 1169, 1033;

¹H NMR (600 MHz, CDCl₃) δ 7.64 (d, J = 9.0 Hz, 1 H), 7.48 (d, J = 2.5 Hz, 1 H), 7.16 (dd, J = 9.0, 2.8 Hz, 1 H), 3.97 (s, 2 H), 3.88 – 3.81 (m, 5 H), 2.06 (bs, 4 H);

¹³C NMR (151 MHz, CDCl₃) δ 155.9, 143.0, 136.9, 123.4, 119.4, 111.6, 56.1, 51.3, 47.6, 24.2, 23.5.

**Compound 5.7**: Prepared from 5.5 (740.8 mg, 2.75 mmol, 1 equiv) following the GP2. The product was isolated in 75% yield (600.1 mg) after column chromatography (silica gel, 10:1 hexanes/EtOAc).

**Physical state**: brown solid;

R_f = 0.26 (4:1 hexanes/EtOAc);

m.p. = 48–50 °C;

HRMS (m/z): calcd for C₁₀H₁₂ClN₃O₃SH⁺ [M+H]⁺, 290.0361; found, 290.0361;

IR (film) ν_max = 2858, 1583, 1567, 1411, 1361, 1302, 1173, 1107, 1015;

¹H NMR (600 MHz, CDCl₃) δ 8.03 (d, J = 8.1 Hz, 1 H), 7.70 (d, J = 8.1 Hz, 1 H), 7.64 (t, J = 7.7 Hz, 1 H), 7.29 (t, J = 7.7 Hz, 1 H), 4.10 (s, 2H), 3.98 – 3.88 (m, 4 H), 3.84 (s, 2 H);

¹³C NMR (151 MHz, CDCl₃) δ 147.8, 137.4, 135.9, 128.9, 125.3, 118.4, 67.3, 65.9, 52.2, 45.1.

**Compound 2.50**: A 5 mL vial equipped with a stir bar, previously flame-dried under vacuum and cooled under an atmosphere of Ar, was charged with menthol (190 mg, 1.22 mmole, 1 equiv), triazene sulfonyl
chlorine 2.59 (500 mg, 1.831 mmole, 1.25 equiv) and DMAP (75 mg, 0.61 mmole, 0.5 equiv). These solids were then dissolved in pyridine (1.22 mL, 1 M) and the reaction was allowed to proceed at room temperature under Ar for 48 h (TLC control). The resulting suspension was diluted with EtOAc (3 mL) and washed with H₂O (2 mL). The layers were then partitioned and the aqueous solution was further extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over MgSO₄, filtrated and concentrated in vacuo. The crude mixture was purified by flash chromatography (silica gel, 10:1 hexanes/EtOAc) to give 2.50 as an orange solid (398 mg, 83% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.99 (d, 1 H), 7.57 – 7.46 (m, 2 H), 7.17 (t, J = 6.8 Hz, 1 H), 4.42 (td, J = 10.8, 4.5 Hz, 1 H), 3.96 (t, J = 6.6 Hz, 2 H), 3.86 – 3.71 (m, 2 H), 2.28 – 2.20 (m, 1 H), 2.12 – 1.97 (m, 5 H), 1.65 – 1.60 (m, 2 H), 1.41 – 1.30 (m, 2 H), 1.17 (q, J = 12.0 Hz, 1 H), 1.01 – 0.89 (m, 1 H), 0.86 (d, J = 6.4 Hz, 3 H), 0.80 (d, J = 6.4 Hz, 3 H), 0.45 (d, J = 6.9 Hz, 3 H);

Compounds 2.51, 2.52 and 2.53: A 5 mL vial equipped with a stir bar, previously flame-dried under vacuum and cooled under an atmosphere of Ar, was charged with 2.50 (10 mg, 0.025 mmole, 1 equiv) and CuBr₂ (5.66 mg, 0.025 mole, 1 equiv). The vial was capped and placed under vacuum, before being back-filled with Ar (process repeated 2X). To this, CH₃CN (1 mL) was added to obtain a dark green solution which was heated at 80 ºC for 30
min. The resulting crude mixture was dissolved with EtOAc (3 mL) and washed with a solution of NH₄OH (1 mL, 3X). The organic solution was further washed with water (1 mL) and brine (1 mL), before being dried over MgSO₄, and concentrated in vacuo. The resulting crude mixture was purified by chromatography (silica gel, 20:1 hexanes/EtOAc) to give 4.5 mg (~60% yield) of a mixture of compounds in a ratio determined by integration of the ¹H-NMR spectrum (2.51:2.52:2.53 = 20:26:1).

For 2.51:

¹H NMR (400 MHz, CDCl₃) δ 7.87 (dd, J = 7.6, 1.6 Hz, 2 H), 7.60 (t, J = 7.8 Hz, 1 H), 7.50 (t, J = 7.8 Hz, 2 H), 4.66 (s, 1 H), 4.60 (s, 1 H), 4.48 (td, J = 10.8, 4.5 Hz, 1 H), 2.28–2.20 (m, 1 H), 2.18–2.08 (m, 1 H), 1.71–1.59 (m, 2 H), 1.53–1.44 (m, 1 H), 1.42 (s, 3 H), 1.39–1.18 (m, 3 H), 0.92 (d, J = 6.4 Hz, 3 H).

Compound 2.60: Synthesized from cyclopentyl ethanol (1 mmol) and 2.59 following the protocol described in general procedure GP3 (vide infra).

After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 52% yield (183.3 mg).

¹H NMR (600 MHz, CDCl₃) δ 7.96 (d, J = 7.6 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 1 H), 7.52 (t, J = 7.9 Hz, 1 H), 7.19 (t, J = 7.7 Hz, 1 H), 4.11–4.05 (m, 2 H), 3.97 (d, J = 6.9 Hz, 2 H), 3.81–3.75 (m, 2 H), 2.10–1.99 (m, 4 H), 1.83 (heptet, J = 8.1 Hz, 1 H), 1.71–1.61 (m, 4 H), 1.59–1.52 (m, 2 H), 1.50–1.40 (m, 2 H), 1.06–0.93 (m, 2 H);

¹³C NMR (151 MHz, CDCl₃) δ 149.6, 134.3, 130.6, 128.8, 124.3, 118.0, 77.3, 77.2, 77.1, 77.0, 76.9, 70.3, 51.3, 47.4, 37.5, 36.3, 35.1, 32.4, 25.0, 24.2, 23.5.
**Compound 2.64**: Synthesized from 2,6-dimethyl-heptan-4-ol (2.079 mmol) and 2.59 following the protocol described in *general procedure GP3 (vide infra)*. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 77% yield (612 mg).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.01 – 7.94 (m, 1 H), 7.58 – 7.47 (m, 2 H), 7.17 (ddd, $J = 8.3, 7.1, 1.5$ Hz, 1 H), 4.67 (quintet, $J = 6.4$ Hz, 1 H), 3.97 (t, $J = 6.6$ Hz, 2 H), 3.80 (t, $J = 6.7$ Hz, 2 H), 2.13 – 1.95 (m, 4 H), 1.72 – 1.55 (m, 2 H), 1.36 (ddd, $J = 13.7, 7.4, 5.8$ Hz, 2 H), 0.78 (t, $J = 6.4$ Hz, 12 H).

**Compounds 2.65 and 2.66**: A 20 mL vial equipped with a stir bar, previously flame-dried under vacuum and cooled under an atmosphere of Ar, was charged with 2.64 (106.2 mg, 0.278 mmole, 1 equiv) and CuBr$_2$ (15.6 mg, 0.069 mole, 0.25 equiv). The vial was capped and placed under vacuum, before being back-filled with Ar (process repeated 2X). To this, CH$_3$CN (11.2 mL) was added to obtain a dark green solution which was heated at 80 ºC for 3h. The resulting crude mixture was dissolved with EtOAc (3 mL) and washed with a 0.05M NaEDTA solution (5 mL, 3X). The organic solution was further washed with brine (5 mL), before being dried over MgSO$_4$, and concentrated *in vacuo*. The resulting crude mixture was purified by chromatography (silica gel, 20:1 hexanes/EtOAc) to give 35.4 mg (~42% yield) of a mixture of compounds in a ratio determined by integration of the $^1$H-NMR spectrum (2.65:2.66 = 3:1). A second fraction was isolated from the column (9.7 mg, ~10% yield) that
was identified as 2.67.

For 2.67:

Rf = 0.2 (2:1 hexanes/EtOAc);

1H NMR (400 MHz, CDCl3) δ 4.96 (d, J = 9.5 Hz, 1 H), 4.16 – 4.01 (m, 1 H), 1.96 (s, 3 H), 1.66 – 1.58 (m, 2 H), 1.31 – 1.21 (m, 4 H), 0.91 (ddt, J = 13.1, 6.6, 1.3 Hz, 12 H).

13C NMR (151 MHz, CDCl3) δ 169.4, 45.8, 45.7, 25.1, 23.7, 23.3, 22.4.

Compound 2.74: A 5 mL vial equipped with a stir bar, previously flame-dried under vacuum and cooled under an atmosphere of Ar, was charged with 2.64 (25.3 mg, 0.066 mmole, 1 equiv) and CuBr2 (3.7 mg, 0.016 mole, 0.25 equiv). The vial was capped and placed under vacuum, before being back-filled with Ar (process repeated 2X). To this, CCl4 (2.6 mL) was added to obtain a heterogeneous solution which was heated at 80 ºC for 3h. The resulting crude mixture was concentrated in vacuo, and then dissolved with EtOAc (3 mL) and washed with a 0.05M NaEDTA solution (5 mL, 3X). The organic solution was further washed with brine (5 mL), before being dried over MgSO4, and concentrated in vacuo. The resulting crude mixture was purified by chromatography (silica gel, 20:1 hexanes/EtOAc) to give 13.3 mg (~63% yield) of a mixture of compounds in a ratio determined by integration of the 1H-NMR spectrum (2.74:2.65:2.66 = 20:2:1).

For 2.74:
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.93 (d, $J = 8.6$ Hz, 3 H), 7.70 – 7.62 (m, 1 H), 7.55 (t, $J =$ 7.8 Hz, 3 H), 5.08 – 4.84 (m, 1 H), 2.17 (dd, $J =$ 15.4, 5.7 Hz, 1 H), 2.09 (dd, $J =$ 15.4, 4.7 Hz, 1 H), 1.62 – 1.53 (m, 6 H), 0.89 (dd, $J =$ 10.6, 6.1 Hz, 3 H), 0.80 (dd, $J =$ 12.1, 6.1 Hz, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 137.8, 133.7, 129.3, 127.9, 80.7, 68.3, 50.2, 45.1, 34.3, 31.8, 24.6, 22.6, 22.4.

**General procedure for the synthesis of alkyl triazine tosylates/tosylamines (GP3)**

A 5 mL vial equipped with a stir bar, previously flame-dried under vacuum and cooled under an atmosphere of Ar, was charged with the alcohol/amine (1 equiv) and Tz$^\circ$Cl 3.3 (1.25 equiv) which were then dissolved in CH$_2$Cl$_2$ (0.5 M). To this mixture DMAP (2 equiv) was added$^2$ and the reaction was allowed to proceed at room temperature under Ar for 16–24 h (TLC control). The resulting suspension was diluted with EtOAc (3 mL) and washed with H$_2$O (2 mL). The layers were then partitioned and the aqueous solution was further extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over MgSO$_4$, filtrated and concentrated in vacuo. The product was purified by flash chromatography (silica gel, hexanes/EtOAc).

---

$^2$ When the amine•HCl salt is used, 4 equiv of DMAP are used.
**Compound 2.79:** Synthesized from 2,6-dimethyl-heptan-4-ol (0.400 mmol) following the *general procedure GP3*. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 92% yield (143.3 mg).

**Physical state:** yellow oil;

$R_f = 0.58$ (4:1 hexanes/EtOAc);

**HRMS (m/z):** calcd for C$_{20}$H$_{35}$N$_3$O$_3$SH$^+ [M+H]^+$, 398.2472; found, 398.2480;

**IR (film) $\nu_{\text{max}} = 2957, 2870, 1593, 1466, 1388, 1350, 1270, 1174, 1109, 922, 890$;**

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.85 (d, $J = 8.0$ Hz, 1 H), 7.36 (s, 1 H), 6.97 (d, $J = 8.0$ Hz, 1 H), 4.65 – 4.58 (m, 1 H), 3.83 (q, $J = 7.1$ Hz, 4 H), 2.39 (s, 3 H), 1.65 – 1.51 (m, 4 H), 1.39 – 1.21 (m, 8 H), 0.83 – 0.70 (m, 12 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 149.2, 144.8, 130.1, 128.0, 125.0, 118.3, 81.3, 49.4, 44.1, 42.4, 24.3, 22.8, 22.4, 21.8, 14.7, 11.5.

**Compound 3.19:** Synthesized from 5-methyl-1-phenylhexan-3-ol (0.330 mmol) following the *general procedure GP3*. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 85% yield (124.8 mg).

**Physical state:** yellow oil;

$R_f = 0.52$ (4:1 hexanes/EtOAc);

**HRMS (m/z):** calcd for C$_{24}$H$_{35}$N$_3$O$_3$SH$^+ [M+H]^+$, 446.2472; found, 446.2493;

**IR (film) $\nu_{\text{max}} = 2956, 2935, 2870, 1593, 1454, 1388, 1351, 1270, 1174, 1109, 889$;**

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.84 (d, $J = 8.1$ Hz, 1 H), 7.38 (s, 1 H), 7.22 (t, $J = 7.4$ Hz, 2
H), 7.15 (t, J = 7.2 Hz, 1 H), 7.00 – 6.96 (m, 3 H), 4.65 (t, J = 6 Hz, 1 H), 3.86 – 3.79 (m, 4 H), 2.62 – 2.49 (m, 2 H), 2.39 (s, 3 H), 1.90 – 1.80 (m, 2 H), 1.68 – 1.58 (m, 2 H), 1.41 – 1.31 (m, 4 H), 1.28 (t, J = 6.6 Hz, 3 H), 0.78 (dd, J = 11.9, 6.1 Hz, 6 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 149.2, 144.9, 141.6, 130.2, 128.4, 128.4, 127.9, 126.0, 125.1, 118.4, 81.9, 49.4, 43.3, 42.4, 36.4, 30.7, 24.4, 22.8, 22.4, 21.8, 14.6, 11.5.

**Compound 5.8:** Synthesized from 5-methyl-1-phenylhexan-3-ol (0.300 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexane/EtOAc), the product was obtained in 86% yield (109.4 mg).

**Physical state:** yellow oil;

$R_f$ = 0.60 (4:1 hexane/EtOAc);

**HRMS (m/z):** calcd for C$_{22}$H$_{39}$N$_{3}$O$_{3}$SH$^{+}$ [M+H]$^{+}$, 426.2785; found, 426.2795;

**IR (film) $\nu_{\text{max}}$** = 2955, 2870, 1594, 1466, 1388, 1351, 1270, 1175, 1109, 888;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.85 (d, J = 8.0 Hz, 1 H), 7.36 (s, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 4.64 – 4.57 (m, 1 H), 3.82 (q, J = 7.0 Hz, 4 H), 2.38 (s, 3 H), 1.66 – 1.48 (m, 3 H), 1.41 – 1.23 (m, 9 H), 1.24 – 1.11 (m, 2 H), 0.98 (dd, J = 14.8, 7.3 Hz, 2 H), 0.82 – 0.73 (m, 12 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 149.1, 144.7, 130.1, 128.1, 125.0, 118.3, 82.7, 49.4, 43.4, 42.4, 38.8, 34.9, 27.9, 24.3, 22.9, 22.6, 22.6, 22.3, 22.2, 21.8, 14.7, 11.5.

**Compound 5.9:** Synthesized from 2-methylnon-8-en-4-ol (0.300 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexane/EtOAc), the product was obtained in 73%
yield (89.7 mg).

**Physical state**: yellow oil;

\[ R_f = 0.60 \text{ (4:1 hexanes/EtOAc)}; \]

**HRMS (m/z)**: calcd for C_{21}H_{35}N_{3}O_{3}SH^{+} [M+H]^+, 410.2472; found, 410.2470;

**IR (film) \nu_{\text{max}} = 2956, 2934, 2870, 1593, 1465, 1388, 1349, 1327, 1270, 1256, 1173, 1108, 992;**

\[ ^1H \text{ NMR (600 MHz, CDCl}_3) \delta 7.85 (d, J = 8.1 \text{ Hz}, 1 \text{ H}), 7.36 (s, 1 \text{ H}), 6.98 (d, J = 8.1 \text{ Hz}, 1 \text{ H}), 5.66 (dq, J = 12.2, 6.8 \text{ Hz}, 1 \text{ H}), 4.94 - 4.85 (m, 2 \text{ H}), 4.65 - 4.57 (m, 1 \text{ H}), 3.88 - 3.76 (m, 4 \text{ H}), 2.39 (s, 3 \text{ H}), 1.90 (q, J = 7.0 \text{ Hz}, 2 \text{ H}), 1.63 - 1.52 (m, 3 \text{ H}), 1.40 - 1.22 (m, 9 \text{ H}), 0.96 - 0.82 (m, 1 \text{ H}), 0.76 (dd, J = 18.5, 6.1 \text{ Hz}, 6 \text{ H}); \]

\[ ^{13}C \text{ NMR (151 MHz, CDCl}_3) \delta 149.2, 144.8, 138.4, 130.1, 128.0, 125.0, 118.4, 114.8, 82.3, 49.4, 43.3, 42.4, 34.0, 33.5, 24.3, 23.6, 22.9, 22.3, 21.8, 14.7, 11.5. \]

**Compound 5.10**: Synthesized from 3,7-dimethyl-octan-1-ol (0.410 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 93% yield (158.1 mg).

**Physical state**: orange oil;

\[ R_f = 0.55 \text{ (4:1 hexanes/EtOAc)}; \]

**HRMS (m/z)**: calcd for C_{21}H_{37}N_{3}O_{3}SH^{+}[M+H]^+, 412.2628; found, 412.2612;

**IR (film) \nu_{\text{max}} = 2954, 2927, 1466, 1389, 1353, 1176;**

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta 7.85 (d, J = 8.1 \text{ Hz}, 1 \text{ H}), 7.37 (s, 1 \text{ H}), 6.99 (d, J = 7.9 \text{ Hz}, 1 \text{ H}), 4.10 - 4.02 (m, 2 \text{ H}), 3.83 (q, J = 7.2 \text{ Hz}, 4 \text{ H}), 2.39 (s, 3 \text{ H}), 1.70 - 1.59 (m, 1 \text{ H}), 1.53 -
1.32 (m, 6 H), 1.28 (t, \( J = 7.1 \) Hz, 3 H), 1.24 – 0.98 (m, 6 H), 0.84 (d, \( J = 6.6 \) Hz, 6 H), 0.78 (d, \( J = 6.6 \) Hz, 3 H);

\( ^{13}C \) NMR (151 MHz, CDCl\(_3\)) \( \delta \) 149.3, 145.1, 130.7, 126.2, 125.2, 118.4, 68.8, 49.4, 42.4, 39.3, 37.0, 36.0, 29.3, 28.0, 24.6, 22.8, 22.7, 21.8, 19.3, 14.6, 11.5.

**Compound 5.11:** Synthesized from 3-ethylpentanol (0.250 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 93% yield (85.4 mg).

**Physical state:** yellow oil;

\( R_f = 0.54 \) (4:1 hexanes/EtOAc);

HRMS (m/z): calcd for C\(_{18}\)H\(_{31}\)N\(_3\)O\(_3\)SH\(^+\) [M+H]\(^+\), 370.2159; found, 370.2161;

IR (film) \( \nu_{\text{max}} \) = 2963, 2934, 1465, 1389, 1351, 1174, 1110, 966, 810, 671;

\(^1H\) NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.84 (d, \( J = 8.1 \) Hz, 1 H), 7.38 (s, 1 H), 6.99 (d, \( J = 8.0 \) Hz, 1 H), 4.05 (t, \( J = 6.5 \) Hz, 2 H), 3.83 (q, \( J = 6.7 \) Hz, 4 H), 2.39 (s, 3 H), 1.60 – 1.53 (m, 2 H), 1.36 (t, \( J = 7.2 \), 3 H), 1.31 – 1.25 (m, 4 H), 1.18 – 1.04 (m, 4 H), 0.79 (t, \( J = 7.2 \) Hz, 6 H);

\( ^{13}C \) NMR (151 MHz, CDCl\(_3\)) \( \delta \) 149.3, 145.2, 130.6, 126.2, 125.1, 118.3, 68.9, 49.4, 42.4, 36.5, 32.0, 25.0, 21.8, 14.6, 11.4, 10.6.

**Compound 2.82:** Synthesized from 2-cyclopentylethanol (0.500 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 90% yield (165.9 mg).
Physical state: yellow oil;

$R_f = 0.53$ (4:1 hexanes/EtOAc);

HRMS ($m/z$): calcd for C$_{18}$H$_{29}$N$_3$O$_3$SH$^+ [M+H]^+$, 368.2002; found, 368.2004;

IR (film) $\nu_{\text{max}} = 2940, 2868, 1593, 1388, 1349, 1327, 1173, 1109, 967, 930, 671$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 8.1$ Hz, 1 H), 7.37 (s, 1 H), 6.99 (d, $J = 8.0$ Hz, 1 H), 4.02 (t, $J = 6.7$ Hz, 2 H), 3.86 – 3.78 (m, 4 H), 2.39 (s, 3 H), 1.88 – 1.74 (m, 1 H), 1.70 – 1.60 (m, 4 H), 1.59 – 1.50 (m, 2 H), 1.49 – 1.40 (m, 2 H), 1.35 (t, $J = 7.2$ Hz, 3 H), 1.27 (t, $J = 7.1$ Hz, 3 H), 1.04 – 0.94 (m, 2 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 149.3, 145.2, 130.7, 125.9, 125.1, 118.3, 69.9, 49.4, 42.4, 36.2, 35.0, 32.4, 25.0, 21.8, 14.6, 11.4.

**Compound 5.12:** Synthesized from 2-cyclohexylethanol (0.500 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 89% yield (168.9 mg).

Physical state: yellow oil;

$R_f = 0.53$ (4:1 hexanes/EtOAc);

HRMS ($m/z$): calcd for C$_{19}$H$_{31}$N$_3$O$_3$SH$^+ [M+H]^+$, 382.2159; found, 382.2168;

IR (film) $\nu_{\text{max}} = 2922, 2850, 1593, 1448, 1388, 1349, 1172, 1108, 961, 907, 671$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.84 (d, $J = 8.1$ Hz, 1 H), 7.38 (s, 1 H), 6.99 (d, $J = 8.0$ Hz, 1 H), 4.05 (t, $J = 6.5$ Hz, 2 H), 3.83 (q, $J = 6.7$ Hz, 4 H), 2.39 (s, 3 H), 1.62 (d, $J = 10.9$ Hz, 3 H), 1.55 (d, $J = 14.2$ Hz, 3 H), 1.48 (q, $J = 6.5$ Hz, 2 H), 1.40 – 1.24 (m, 6 H), 1.18 – 1.04 (m, 3 H), 0.79 (q, $J = 11.7$ Hz, 2 H);
$^{13}\text{C NMR (151 MHz, CDCl}_3\text{)}$ δ 149.3, 145.1, 130.7, 126.1, 125.1, 118.3, 68.4, 49.4, 42.4, 36.3, 33.7, 32.9, 26.5, 26.2, 21.8, 14.6, 11.4.

**Compound 4.13**: Synthesized from (1$R$, 2$S$, 5$R$)-($-$)-menthol (0.400 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 99% yield (162.0 mg).

**Physical state**: thick yellow oil;

$R_f = 0.58$ (4:1 hexanes/EtOAc);

$[\alpha]_D = -108.8^\circ$ ($c = 0.50,$ CH$_2$Cl$_2$);

**HRMS ($m/z$)**: calcd for C$_{21}$H$_{35}$N$_3$O$_3$SH$^+ \ [M+H]^+$, 410.2472; found, 410.2482;

**IR (film)** $\nu_{\text{max}} = 2955, 2931, 2870, 1593, 1388, 1351, 1174, 943, 913, 867, 674$;

$^1\text{H NMR (600 MHz, CDCl}_3\text{)}$ δ 7.85 (d, $J = 8.1$ Hz, 1 H), 7.36 (s, 1 H), 6.97 (d, $J = 8.1$ Hz, 1 H), 4.35 (td, $J = 10.8,$ 4.5 Hz, 1 H), 3.86 – 3.67 (m, 4 H), 2.38 (s, 3 H), 2.19 (d, $J = 12.2$ Hz, 1 H), 2.04 – 1.96 (m, 1 H), 1.60 (d, $J = 14.6$ Hz, 2 H), 1.40 – 1.22 (m, 8 H), 1.18 – 1.09 (m, 1 H), 0.98 – 0.87 (m, 1 H), 0.85 (d, $J = 6.5$ Hz, 3 H), 0.83 – 0.74 (m, 4 H), 0.42 – 0.34 (d, $J = 6.5$ Hz, 3 H);

$^{13}\text{C NMR (151 MHz, CDCl}_3\text{)}$ δ 149.2, 144.8, 130.0, 127.9, 125.1, 118.3, 83.4, 49.4, 47.8, 42.3, 42.0, 33.9, 31.7, 25.1, 22.9, 22.0, 21.8, 21.0, 15.1, 14.7, 11.5.
Compound 5.13: Synthesized from menthylamine\(^3\) (0.230 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 74\% yield (69.5 mg).

**Physical state:** pale yellow solid;

\(R_f = 0.28\) (5:1 hexanes/EtOAc);

**HRMS (m/z):** calcd for \(C_{21}H_{36}N_4O_2SH^+ \[M+H]^+\), 409.2632; found, 409.2638;

**IR (film) \(\nu_{\max}\):** 2953, 2927, 1455, 1393, 1337, 1269, 1165;

**\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\):** 7.81 (d, \(J = 8.0\) Hz, 1 H), 7.35 (s, 1 H), 7.00 (d, \(J = 7.3\) Hz, 1 H), 5.24 (d, \(J = 8.5\) Hz, 1 H), 3.89 – 3.77 (m, 3 H), 3.76 – 3.68 (m, 1 H), 3.22 – 3.14 (m, 1 H), 2.38 (s, 3 H), 2.30 – 2.19 (m, 1 H), 1.76 (d, \(J = 12.6\) Hz, 1 H), 1.61 (d, \(J = 10.0\) Hz, 2 H), 1.41 – 1.22 (m, 8 H), 1.04 – 0.91 (m, 2 H), 0.85 (d, \(J = 7.0\) Hz, 3 H), 0.77 – 0.61 (m, 7 H);

**\(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\):** 147.2, 143.4, 132.3, 127.7, 125.5, 118.2, 55.4, 49.9, 48.9, 43.4, 42.2, 34.4, 31.9, 25.9, 23.8, 22.2, 21.8, 21.3, 15.4, 14.6, 11.5.

Compound 3.17: In a 5 mL vial equipped with a stir bar, the 2,7-dimethyl-4-amino-heptane (107 mg, 0.750 mmol, 1.4 equiv) was added and dissolved in CH\(_2\)Cl\(_2\) (2 mL). To this mixture a solution of saturated NaHCO\(_3\) (2 mL) was added followed by 3.3 (155 mg, 0.535 mmol, 1 equiv). The resulting biphasic mixture was then stirred vigorously at room temperature for 45 min. Upon completion (TLC control), the organic layer was separated, washed with brine (2

---

\(^3\) Schopohl, M.C.; Bergander, K.; Kataeva, O.; Fröhlich, R.; Waldvogel, S. R. *Synthesis* 2003, (17), 2689.
mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. After purification on silica gel (20:1 hexanes/EtOAc), the product was obtained in 94% yield (199.5 mg).

**Physical state**: white solid;

$R_f = 0.56$ (4:1 hexanes/EtOAc);

m.p. = 64–66 ºC;

**HRMS (m/z)**: calcd for C$_{20}$H$_{36}$N$_4$O$_2$SH$^+ [M+H]^+$, 397.2632; found, 397.2631;

**IR (film)** $\nu_{max}$ = 2956, 2869, 1594, 1393, 1329, 1270, 1166, 1138, 1112, 1061;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.81 (d, $J = 8.0$ Hz, 1 H), 7.35 (s, 1 H), 6.99 (d, $J = 8.4$ Hz, 1 H), 5.14 (d, $J = 8.0$ Hz, 1 H), 3.89 – 3.80 (m, 2 H), 3.80 – 3.73 (m, 2 H), 3.37 (sextet, $J = 6.6$ Hz, 1 H), 2.38 (s, 3 H), 1.60 (heptet, $J = 6.7$ Hz, 2 H), 1.37 (t, $J = 12.5$ Hz, 3 H), 1.28 (t, $J = 13.5$ Hz, 3 H), 1.19 – 1.14 (m, 4 H), 0.74 (m, 12 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 147.3, 143.5, 131.8, 128.1, 125.4, 118.2, 51.5, 49.9, 45.6, 42.1, 24.6, 22.8, 22.4, 21.7, 14.6, 11.4.

**Compound 5.14**: Synthesized from L-leucine methyl ester hydrochloride (0.250 mmol) following the *general procedure GP3* (4 equiv of DMAP were used). After purification on silica gel (4:1 hexanes/EtOAc), the product was obtained in 93% yield (92.4 mg).

**Physical state**: pale yellow solid;

$R_f = 0.48$ (2:1 hexanes/EtOAc);

$[\alpha]_D = +344.7^\circ$ (c = 0.34, CH$_2$Cl$_2$);

m.p. = 55–57 ºC;

**HRMS (m/z)**: calcd for C$_{18}$H$_{30}$N$_4$O$_4$SH$^+ [M+H]^+$, 399.2060; found, 399.2063;
IR (film) $\nu_{\text{max}} =$ 3272, 2957, 1742, 1593, 1467, 1393, 1339, 1270, 1167, 1139, 1112;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J = 8.0$ Hz, 1 H), 7.39 (s, 1 H), 6.97 (d, $J = 8.0$ Hz, 1 H), 6.18 (d, $J = 9.1$ Hz, 1 H), 4.04 (q, $J = 7.8$ Hz, 1 H), 3.93 – 3.83 (m, 3 H), 3.77 (td, $J = 14.1$, 7.1 Hz, 1 H), 3.32 (s, 3 H), 2.37 (s, 3 H), 1.82 – 1.73 (m, 1 H), 1.55 – 1.47 (m, 2 H), 1.37 (dt, $J = 16.7$, 7.2 Hz, 6 H), 0.89 (dd, $J = 6.4$, 4.0 Hz, 6 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 172.5, 147.6, 144.0, 129.5, 128.3, 125.1, 117.9, 55.0, 52.0, 49.9, 42.7, 42.3, 24.4, 22.6, 22.0, 21.8, 14.6, 11.3.

**Compound 5.15:** Synthesized from D-leucine tert-butyl ester hydrochloride (0.223 mmol) following the *general procedure GP3* (4 equiv of DMAP were used). After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 99% yield (97.2 mg).

**Physical state:** pale yellow solid;

$R_f = 0.37$ (4:1 hexanes/EtOAc);

$[\alpha]_D = -383.1^\circ$ (c = 0.13, CH$_2$Cl$_2$);

m.p. = 78–80 °C;

HRMS ($m/z$): calcd for C$_{21}$H$_{36}$N$_4$O$_4$SH$^+$ [M+H$^+$], 441.2530; found, 441.2530;

IR (film) $\nu_{\text{max}} =$ 2959, 1731, 1393, 1340, 1167, 1137;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.77 (d, $J = 8.0$ Hz, 1 H), 7.36 (s, 1 H), 6.96 (d, $J = 8.1$ Hz, 1 H), 6.15 (d, $J = 9.3$ Hz, 1 H), 3.93 (dd, $J = 15.3$, 8.7 Hz, 1 H), 3.90 – 3.76 (m, 4 H), 2.36 (s, 3 H), 1.85 – 1.75 (m, 1 H), 1.50 – 1.41 (m, 2 H), 1.37 (dd, $J = 16.7$, 7.3 Hz, 6 H), 1.14 (s, 9 H), 0.92 (dd, $J = 6.6$, 2.9 Hz, 6 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 171.5, 147.8, 143.9, 130.2, 128.3, 125.1, 118.0, 81.6, 55.7,
Compound 5.16: Synthesized from L-valine methyl ester hydrochloride (0.500 mmol) following the general procedure GP3 (4 equiv of DMAP were used). After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 99% yield (190.5 mg).

Physical state: pale yellow solid;

$R_f = 0.28$ (4:1 hexanes/EtOAc);

$[\alpha]_D = +440.0^\circ$ (c = 0.49, CH$_2$Cl$_2$);

m.p. = 89–91 °C;

HRMS ($m/z$): calcd for C$_{17}$H$_{28}$N$_4$O$_4$SH$^+$ [M+H]$^+$, 385.1904; found, 385.1914;

IR (film) $\nu_{\text{max}}$ = 2969, 1741, 1467, 1393, 1340, 1269, 1167;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.73 (d, $J = 8.0$ Hz, 1 H), 7.38 (s, 1 H), 6.96 (d, $J = 8.1$ Hz, 1 H), 6.27 (d, $J = 9.2$ Hz, 1 H), 3.95 – 3.82 (m, 4 H), 3.81 – 3.74 (m, 1 H), 3.33 (s, 3 H), 2.37 (s, 3 H), 2.04 – 1.97 (m, 1 H), 1.37 (dt, $J = 11.1$, 7.2 Hz, 6 H), 0.94 (t, $J = 7.8$ Hz, 6 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 171.7, 147.6, 144.0, 129.7, 128.2, 125.1, 117.9, 61.7, 51.8, 49.9, 42.3, 32.0, 21.8, 18.8, 18.0, 14.6, 11.4.

Compound (–)-3.21: Synthesized from commercially available $(R)$-(-)-1-cyclohexylethylamine (94% ee) (0.480 mmol) following the general procedure GP3. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 99% yield (180.8 mg).

Physical state: pale yellow solid;
\( R_f = 0.30 \) (4:1 hexanes/EtOAc);

\( [\alpha]_D = -194^\circ \) (c = 0.42, CH\(_2\)Cl\(_2\));

m.p. = 77–79 °C;

**HRMS (m/z):** calcd for C\(_{19}\)H\(_{32}\)N\(_4\)O\(_2\)SH\(^+\) [M+H]\(^+\), 381.2319; found, 381.2323;

**IR (film)** \( \nu_{\text{max}} \) = 2925, 2852, 1593, 1450, 1391, 1328, 1269, 1165, 1111, 684;

**\(^1\)H NMR (600 MHz, CDCl\(_3\))** \( \delta \) 7.81 (d, \( J = 8.0 \) Hz, 1 H), 7.34 (s, 1 H), 7.00 (d, \( J = 7.9 \) Hz, 1 H), 5.31 (d, \( J = 7.9 \) Hz, 1 H), 3.88 – 3.78 (m, 3 H), 3.73 – 3.66 (m, 1 H), 3.23 (dq, \( J = 13.9, 6.8 \) Hz, 1 H), 2.38 (s, 3 H), 1.70 (d, \( J = 10.3 \) Hz, 3 H), 1.66 – 1.57 (m, 2 H), 1.37 (t, \( J = 7.2 \) Hz, 3 H), 1.34 – 1.28 (m, 4 H), 1.18 – 1.01 (m, 4 H), 0.98 – 0.88 (m, 1 H), 0.85 (d, \( J = 6.8 \) Hz, 3 H);

**\(^{13}\)C NMR (151 MHz, CDCl\(_3\))** \( \delta \) 147.3, 143.6, 131.1, 128.3, 125.5, 118.3, 54.8, 49.9, 43.8, 42.2, 28.8, 28.2, 26.5, 26.3, 26.2, 21.8, 17.2, 14.6, 11.4.

**Compound 3.27:** Synthesized from dihydrojunenol\(^4\) following a modified procedure: In a 5 mL microwave vial, equipped with a stir bar and previously flame dried under vacuum and cooled under an atmosphere of Ar, dihydrojunenol (28.7 mg, 0.128 mmol, 1 equiv) and 3.3 (148.0 mg, 0.592 mmol, 4 equiv) were dissolved in CH\(_2\)Cl\(_2\) (0.25 mL). To this mixture DMAP (94.0 mg, 0.768 mmol, 6 equiv) was added and the reaction was allowed to proceed at room temperature under Ar for 4 days. In order to drive the reaction to completion, more triazine tosyl chloride 3.3 (75.0 mg, 0.256 mmol, 2 equiv) and DMAP (50.0 mg, 0.384 mmol, 3 equiv) were added and the mixture was stirred at room temperature for another 3 days

\(^4\) Chen, K.; Baran, P. S. *Nature* 2009, 459, 824.
(TLC control). The resulting suspension was diluted with EtOAc (2 mL) and washed with H2O (2 mL). The layers were then partitioned and the aqueous solution was further extracted with EtOAc (3 x 3 mL). The organic mixture was dried over MgSO4, filtrated and concentrated in vacuo. After purification on silica gel (10:1 hexanes/EtOAc), the product was isolated in 65% yield (39.7 mg).

An alternative method for the synthesis of 3.27 is the following: To a solution of dihydrojunenol (10 mg, 0.044 mmol, 1 equiv) in dry THF (0.25 mL) cooled at 0 ºC, a solution of nBuLi (2.4 M, 23 mL, 1.2 equiv) was added dropwise. The resulting mixture was stirred at 0 ºC for 20 mins before a solution of Tz"Cl 3.3 (19.4 mg, 0.066 mmol, 1.5 equiv) in THF (50 µL) was added and as a result the reaction mixture turned dark red. The reaction proceeded overnight at 4 ºC before being quenched with saturated NH4Cl (2 mL) and extracted with EtOAc (3 x 3 mL). The organic solution was washed with brine, dried over MgSO4, filtered and concentrated in vacuo to give a crude mixture. The product 3.27 was isolated by pTLC (silica gel, 8:6:1 toluene/hexanes/Et2O) in 66% yield (14.1 mg).

**Physical state:** thick orange oil;

\[ R_f = 0.50 \text{ (6:1 hexanes/EtOAc);} \]

\[ [\alpha]_D = +37.8^\circ \text{ (c = 0.23, CH}_2\text{Cl}_2); \]

**HRMS \( m/z \):** calcd for C26H43N3O3SH+ [M+H]+, 478.3098; found, 478.3084;

**IR (film) \( \nu_{\text{max}} \):** 2926, 2850, 1593, 1465, 1388, 1343, 1172, 1109, 901;

**\( ^1\text{H NMR (600 MHz, CDCl}_3 \):** 7.77 (d, \( J = 8.1 \) Hz, 1 H), 7.34 (s, 1 H), 6.93 (d, \( J = 8.0 \) Hz, 1 H), 4.92 (t, \( J = 10.6 \) Hz, 1 H), 3.88 – 3.79 (m, 3 H), 3.78 – 3.70 (m, 1 H), 2.37 (s, 3 H), 2.09 – 1.99 (m, 1 H), 1.91 (s, 1 H), 1.59 (q, \( J = 13.8 \) Hz, 1 H), 1.49 (bd, \( J = 13.8 \) Hz, 1 H), 1.46 – 1.30 (m, 8 H), 1.30 – 1.20 (m, 6 H), 1.04 (bq, \( J = 13.9 \) Hz, 2 H), 0.87 (bs, 6 H), 0.79 (s, 3 H),
0.78 (s, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 148.4, 144.1, 129.8, 128.6, 124.7, 117.7, 86.1, 52.7, 50.7, 49.5, 43.8, 42.6, 42.2, 36.2, 33.3, 27.3, 26.1, 21.8, 21.5, 20.7, 18.7, 17.1, 15.7, 14.8, 14.7, 11.5.

**Compound 3.29**: Synthesized from (+)-dehydroabietylamine acetate (0.300 mmol) following the general procedure GP3. After purification on silica gel (4:1 hexanes/EtOAc), the product was obtained in 84% yield (119.6 mg).

**Physical state**: pale yellow solid;

$R_f$ = 0.38 (4:1 hexanes/EtOAc);

$[\alpha]_D = -3.8^\circ$ (c = 0.44, CH$_2$Cl$_2$);

m.p. = 68–70 °C;

**HRMS (m/z)**: calcd for C$_{31}$H$_{46}$N$_4$O$_2$SH$^+$ [M+H]$^+$, 539.3414; found, 539.3411;

**IR (film)** $\nu_{\text{max}}$ = 2958, 1593, 1456, 1391, 1331, 1269, 1163, 1141, 1112, 1063, 821;

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.81 (d, $J$ = 8.0 Hz, 1 H), 7.32 (s, 1 H), 7.14 (d, $J$ = 8.2 Hz, 1 H), 7.02 (d, $J$ = 7.9 Hz, 1 H), 6.96 (d, $J$ = 8.1 Hz, 1 H), 6.85 (s, 1 H), 5.49 (t, $J$ = 7.3 Hz, 1 H), 3.86 – 3.78 (m, 2 H), 3.77 – 3.68 (m, 1 H), 3.67 – 3.57 (m, 1 H), 2.86 – 2.77 (m, 3 H), 2.71 (dd, $J$ = 12.5, 7.2 Hz, 1 H), 2.57 (dd, $J$ = 12.5, 7.7 Hz, 1 H), 2.39 (s, 3 H), 2.27 (d, $J$ = 12.6 Hz, 1 H), 1.77 – 1.68 (m, 2 H), 1.68 – 1.54 (m, 3 H), 1.41 – 1.27 (m, 6 H), 1.28 – 1.16 (m, 12 H), 0.91 (s, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 147.4, 147.2, 145.7, 143.9, 134.9, 129.4, 129.1, 126.9, 125.6, 124.1, 123.8, 118.4, 54.2, 49.8, 44.9, 42.2, 38.4, 37.4, 37.0, 36.1, 33.6, 29.8, 25.2,
Compound 3.32: Synthesized from the corresponding diol\(^5\) (0.057 mmol) following the general procedure GP3. After purification on silica gel (gradient from 4:1 to 2:1 hexanes/EtOAc), the product was obtained in 42% yield (16.8 mg).

Physical state: white solid;

\[ R_f = 0.14 \text{ (4:1 hexanes/EtOAc)}; \]

\[ [\alpha]_D = +71.1^\circ \text{ (c = 0.09, CH}_2\text{Cl}_2); \]

m.p. = 74–76 °C;

HRMS (m/z): calcd for C\(_{41}\)H\(_{65}\)N\(_3\)O\(_4\)SH\(^+\) [M+H]\(^+\), 696.4768; found, 696.4769;

IR (film) \( \nu_{\text{max}} \) = 2928, 1464, 1347, 1173, 907, 729;

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.85 (d, \( J = 8.4 \) Hz, 1 H), 7.33 (s, 1 H), 7.00 (d, \( J = 8.7 \) Hz, 1 H), 5.09 (t, \( J = 3.4 \) Hz, 1 H), 3.93 (d, \( J = 9.4 \) Hz, 1 H), 3.85 – 3.79 (m, 5 H), 3.21 (dd, \( J = 11.4, 4.4 \) Hz, 1 H), 2.39 (s, 3 H), 1.97 – 1.87 (m, 1 H), 1.87 – 1.77 (m, 2 H), 1.77 – 1.67 (m, 2 H), 1.64 – 1.44 (m, 8 H), 1.43 – 1.24 (m, 11 H), 1.23 – 1.17 (m, 2 H), 1.13 – 1.06 (m, 4 H), 0.98 (s, 3 H), 0.96 – 0.90 (m, 7 H), 0.85 (s, 3 H), 0.82 – 0.79 (m, 1 H), 0.78 (s, 3 H), 0.72 (s, 3 H);

\(^13\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \) 149.5, 145.2, 144.0, 130.7, 126.0, 125.1, 122.8, 118.7, 79.1, 74.1, 55.3, 49.3, 47.7, 46.5, 42.3, 41.9, 41.7, 39.9, 38.9, 38.7, 37.0, 36.3, 34.7, 32.7, 32.3, 29.5, 28.2, 28.1, 27.7, 27.3, 27.2, 26.1, 23.6, 21.8, 18.4, 16.8, 15.7, 15.6, 14.6, 11.6.

\(^5\) Bang, E.K.-; Kim, B. H. Tet. Lett. 2009, 50, 2545.
Compound 3.34: The tetrapeptide was prepared with an automated peptide synthesizer using standard procedures. The product was purified by preparative HPLC separation over a Phenomenex Jupiter Proteo 90A column (250 x 21.1 mm) using an elution gradient water/acetonitrile/TFA 91.5:9.4:0.1 → 55:44.9:0.1 over 30 min (retention time for product is 26.3 min) at a flow rate of 10 mL/min. Next, 3.34 is prepared according to the following procedure: the parent tetrapeptide (17.9 mg, 0.040 mmol, 1 equiv) and Tz'Cl 3.3 (17.3 mg, 0.060 mmol, 1.5 equiv) were dissolved in 1:1 CH₂Cl₂/10% aq K₂CO₃ (5 mL) and the resulting heterogeneous solution was stirred at room temperature for two days (monitored by LC-MS). After completion, the crude mixture was extracted with CH₂Cl₂ (5 x 2 mL) and the resulting organic solution was dried over Na₂SO₄, filtered and concentrated in vacuo. The product was isolated in 75% yield (21.0 mg) after chromatography (silica gel, 20:1 CH₂Cl₂/MeOH).

Physical state: white solid;

\( R_f = 0.48 \) (10:1 CH₂Cl₂/MeOH);

\( [\alpha]_D = -95.9^\circ \) (c = 1.0, CHCl₃);

m.p. = 185 °C (decomposition);

HRMS (m/z): calcd for C₃₄H₅₂N₈O₆SH⁺ [M+H]⁺, 701.3803; found, 701.3797;

IR (film) \( \nu_{\text{max}} = 2920, 2851, 1727, 1633, 1463, 1379, 1270, 1121, 1072, 698; \)

\(^1\)H NMR (400 MHz, CDCl₃) \( \delta = 7.63 \) (d, \( J = 6.9 \) Hz, 1 H), 7.48 (bs, 1 H), 7.39 (bd, \( J = 4.8 \) Hz, 1 H), 7.28 (s, 1 H), 7.18 – 6.97 (m, 6 H), 6.04 (bs, 1 H), 5.37 (bs, 1 H), 4.73 (ddd, \( J = 12.1, 8.4, 3.5 \) Hz, 1 H), 4.15 (qd, \( J = 7.4, 4.3 \) Hz, 1 H), 4.01 (t, \( J = 4.8 \) Hz, 1 H), 3.95 – 3.70 (m, 5 H), 3.62 – 3.53 (m, 2 H), 2.87 (dd, \( J = 14.3, 12.3 \) Hz, 1 H), 2.48 (s, 3 H), 2.14 – 2.06 (m, 1 H).
H), 1.67 (ddd, $J = 14.8, 10.8, 3.7$ Hz, 1 H), 1.53 (d, $J = 7.4$ Hz, 3 H), 1.52 – 1.23 (m, 9 H), 0.81 (d, $J = 6.4$ Hz, 3 H), 0.75 (d, $J = 6.9$ Hz, 3 H), 0.63 (d, $J = 6.9$ Hz, 3 H), 0.49 (d, $J = 6.4$ Hz, 3 H);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.3, 174.0, 173.8, 171.0, 148.0, 145.7, 138.5, 129.1, 128.9, 128.1, 126.5, 126.1, 125.4, 118.8, 61.0, 56.7, 54.7, 51.7, 50.1, 42.2, 41.3, 36.7, 28.7, 24.5, 22.9, 21.9, 20.3, 18.5, 17.3, 17.1, 14.4, 11.3.

**General procedures for desaturation**

**General procedure A:** A 20 mL vial adapted with a septum and a stir bar was flame dried under vacuum and kept under an Ar atmosphere. The vial was charged with the SM (0.1 mmol, 1 equiv) and TEMPO (0.1 mmol, 1 equiv) which were dissolved in previously degassed CH$_3$NO$_2$ (4 mL) to give a pale brown solution. To this mixture TFA (0.3 mmol, 3 equiv) was added in one portion and as a result the reaction mixture turned light yellow. The vial was then placed in a preheated oil bath at 60 °C and the reaction was allowed to proceed for 1.5h. Upon completion the solvent was removed *in vacuo* and the resulting crude mixture was dissolved with EtOAc (3 mL) and washed with 1 N HCl (2 mL). After they layers were partitioned, the aqueous solution was further extracted with EtOAc (3 x 3 mL) and the combined organic solution was dried over MgSO$_4$, filtered and concentrated *in vacuo*. The pure product was isolated after flash chromatography (silica gel, hexanes/EtOAc).
**General procedure B:** A 20 mL vial adapted with a septum and a stir bar was flame dried under vacuum and kept under an Ar atmosphere. The vial was charged with the SM (0.1 mmol, 1 equiv) and TEMPO (0.1 mmol, 1 equiv) which were dissolved in previously degassed CH$_3$NO$_2$ (4 mL) to give a pale brown solution. To this mixture TfOH (0.2 mmol, 2 equiv) was added in one portion and as a result the reaction mixture became light yellow in color. The reaction was then stirred at room temperature for 3h under Ar. Upon completion, the solvent was removed *in vacuo* and the resulting crude mixture was dissolved with EtOAc (3 mL) and washed with 1 N HCl (2 mL). After the layers were partitioned, the aqueous solution was further extracted with EtOAc (3 x 3 mL) and the organic solution was dried over MgSO$_4$, filtered and concentrated *in vacuo*. The pure product was isolated after flash chromatography (silica gel, hexanes/EtOAc).

---

**Compound 2.80:** General procedure A was applied, starting with 39.8 mg (0.100 mmol) of 2.79. The crude mixture was purified by flash chromatography (silica gel, 19:1 hexanes/EtOAc) followed by pTLC (19:1 hexanes/EtOAc) to provide 2.80 (13.1 mg) in 44% yield.

**Physical state:** colorless oil;

$R_f$ = 0.70 (4:1 hexanes/EtOAc);

HRMS (m/z): calcd for C$_{16}$H$_{24}$O$_3$SH$^+$ [M+H]$^+$, 297.1519; found, 297.1528;

IR (film) $\nu_{\text{max}}$ = 2958, 1598, 1451, 1363, 1175, 1097, 899, 815, 664;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.80 (d, $J$ = 8.1 Hz, 2 H), 7.32 (d, $J$ = 8.0 Hz, 2 H), 4.77 (s, 1 H), 4.74-4.70 (m, 1 H), 4.67 (s, 1 H), 2.44 (s, 3 H), 2.36 (dd, $J$ = 13.7, 6.9 Hz, 1 H), 2.25 (dd, $J$ = 13.9, 7.5 Hz, 1 H), 1.64 (s, 3 H), 1.62 – 1.56 (m, 1 H), 1.56 – 1.51 (m, 1 H), 1.37 – 1.31
(m, 1 H), 0.86 (d, \(J = 11.9\) Hz, 3 H), 0.76 (d, \(J = 6.5\) Hz, 3 H);

\(^{13}\text{C NMR (151 MHz, CDCl}_3\)) \(\delta\) 144.6, 140.6, 134.7, 129.7, 127.9, 114.5, 80.8, 43.6, 43.2, 24.2, 23.2, 22.6, 21.8.

**Compound 3.4**: *General procedure A* was applied, starting with 44.6 mg (0.1 mmol) of 3.19. The crude mixture was purified by flash chromatography (silica gel, 1:0 to 99:1 hexanes/EtOAc) followed by pTLC (47:3 hexanes/EtOAc) to provide 3.4 (12.3 mg) in 36% yield.

**Physical state**: colorless oil;

\(R_f = 0.52\) (4:1 hexanes/EtOAc);

**HRMS (m/z)**: calcd for \(\text{C}_{20}\text{H}_{24}\text{O}_3\text{SH}^+ [\text{M+H}]^+\), 345.1519; found, 345.1516;

**IR (film)** \(\nu_{\text{max}} = 2987, 1356, 1174, 1055, 1033, 903;\)

\(^1\text{H NMR (600 MHz, CDCl}_3\)) \(\delta\) 7.79 (d, \(J = 7.8\) Hz, 2 H), 7.33 (d, \(J = 7.8\) Hz, 2 H), 7.25 (t, \(J = 7.1\) Hz, 2 H), 7.18 (t, \(J = 7.3\) Hz, 1 H), 7.07 (d, \(J = 7.3\) Hz, 2 H), 4.75 (s, 1 H), 4.72 – 4.65 (m, 2 H), 2.69 – 2.59 (m, 1 H), 2.55 – 2.47 (m, 1 H), 2.46 (s, 3 H), 2.39 (dd, \(J = 14.0, 5.2\) Hz, 1 H), 2.30 (dd, \(J = 13.4, 7.6\) Hz, 1 H), 1.89 – 1.83 (m, 2 H), 1.60 (s, 3 H);

\(^{13}\text{C NMR (151 MHz, CDCl}_3\)) \(\delta\) 144.7, 141.1, 140.4, 134.6, 129.8, 128.6, 128.5, 128.0, 126.2, 114.8, 81.6, 43.0, 35.6, 31.1, 22.5, 21.8.

**Compound 3.5**: *General procedure A* was applied, starting with 42.5 mg (0.100 mmol) of 5.8. The crude mixture was purified by flash chromatography (silica gel, 1:0 to 9:1 hexanes/EtOAc) followed by pTLC (19:1 hexanes/EtOAc) to provide 3.5 (13.3 mg) in 41% yield.
Physical state: colorless oil;

\( R_f = 0.67 \) (4:1 hexanes/EtOAc);

HRMS (m/z): calcd for \( \text{C}_{18}\text{H}_{28}\text{O}_3\text{SH}^+ [\text{M+H}]^+ \), 325.1832; found, 325.1826;

IR (film) \( \nu_{\text{max}} = 2954, 1365, 1176, 899, 815, 664; \)

\(^1\text{H} \) NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.79 (d, \( J = 8.2 \) Hz, 2 H), 7.32 (d, \( J = 7.3 \) Hz, 2 H), 4.75 (s, 1 H), 4.68 (s, 1 H), 4.64 (quintet, \( J = 6.6 \) Hz, 1 H), 2.44 (s, 3 H), 2.37 (dd, \( J = 13.8, 5.8 \) Hz, 1 H), 2.27 (dd, \( J = 13.9, 7.2 \) Hz, 1 H), 1.64 (s, 3 H), 1.60 – 1.52 (m, 2 H), 1.40 (heptet, \( J = 6.6 \) Hz, 1 H), 1.31 – 1.20 (m, 1 H), 1.15 – 1.07 (m, 1 H), 1.06 – 1.00 (m, 2 H), 0.82 – 0.77 (m, 6 H);

\(^1\text{C} \) NMR (151 MHz, CDCl\(_3\)) \( \delta \) 144.5, 140.6, 134.7, 129.7, 128.0, 114.5, 82.5, 43.2, 38.6, 34.2, 27.9, 22.6, 22.6, 22.5, 21.7.

**Compound 3.6:** General procedure A was applied, starting with 41.0 mg (0.100 mmol) of 5.9. The crude mixture was purified by flash chromatography (silica gel, 1:0 to 99:1 hexanes/EtOAc) followed by pTLC (19:1 hexanes/EtOAc) to provide 3.6 (10.6 mg) in 32% yield.

Physical state: colorless oil;

\( R_f = 0.62 \) (4:1 hexanes/EtOAc);

HRMS (m/z): calcd for \( \text{C}_{17}\text{H}_{24}\text{O}_3\text{SNa} [\text{M+Na}]^+ \), 331.1338; found, 331.1339;

IR (film) \( \nu_{\text{max}} = 2960, 1359, 1175, 902, 665; \)

\(^1\text{H} \) NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.78 (d, \( J = 8.2 \) Hz, 2 H), 7.32 (d, \( J = 8.1 \) Hz, 2 H), 5.68 – 5.64 (m, 1 H), 4.97 – 4.89 (m, 2 H), 4.74 (s, 1 H), 4.69 – 4.62 (m, 2 H), 2.44 (s, 3 H), 2.34 (dd, \( J = 13.9, 5.9 \) Hz, 1 H), 2.24 (dd, \( J = 13.9, 7.3 \) Hz, 1 H), 1.99 – 1.90 (m, 2 H), 1.62 (s, 3
H), 1.61 – 1.54 (m, 2 H), 1.46 – 1.36 (m, 1 H), 1.35 – 1.24 (m, 1 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 144.6, 140.5, 138.2, 134.6, 129.8, 127.9, 115.0, 114.6, 82.1, 43.1, 33.4, 33.3, 23.9, 22.5, 21.7.

Compounds 3.7a, b, c: General procedure A was applied, starting with 36.5 mg (0.088 mmol) of 5.10. The crude mixture was purified by flash chromatography (silica gel, 49:1 hexanes/EtOAc) followed by pTLC (6:1 hexanes/EtOAc) to provide 14.9 mg (55% yield) of an unseparable mixture of olefin isomers and reduced product 3.7a:3.7(b+c) = 10:8.7 (NMR ratio).

Physical state: colorless oil;

$R_f$ = 0.57 (4:1 hexanes/EtOAc);

HRMS (m/z): calcd for C$_{17}$H$_{26}$O$_3$SH$^+$ [M+H]$^+$, 311.1675; found, 311.1668;

IR (film) $\nu_{\text{max}}$ = 2954, 2927, 1360, 1188, 1175, 962;

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.83 – 7.74 (m, 12 H), 7.39 – 7.30 (m, 12 H), 5.21 (t, J = 7.2 Hz, 1 H), 5.11 (td, J = 7.1, 1.2 Hz, 2 H), 4.78 (s, 3 H), 4.69 (s, 3 H), 4.16 – 3.99 (m, 14 H), 2.45 (s, 20 H), 2.41 – 2.25 (m, 12 H), 1.99 – 1.84 (m, 12 H), 1.61 (s, 3 H), 1.55 – 1.42 (m, 12 H), 1.39 – 1.29 (m, 7 H), 1.22 – 1.03 (m, 16 H), 0.90 – 0.82 (m, 40 H), 0.82 – 0.78 (m, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 144.8, 144.7, 144.7, 144.7, 144.3, 133.4, 133.3, 133.2, 129.9, 129.9, 129.9, 129.6, 129.0, 128.7, 128.7, 128.0, 128.0, 128.0, 111.9, 69.2, 69.1, 68.9, 68.6, 39.2, 39.1, 38.8, 38.8, 38.6, 36.9, 36.3, 35.8, 35.1, 31.5, 29.3, 28.0, 27.9, 27.7, 25.9, 25.8,
Compounds 3.8a, b, c: General procedure A was applied, starting with 35.4 mg (0.096 mmol) of 5.11. The crude mixture was purified by flash chromatography (silica gel, 49:1 hexanes/EtOAc) to provide 17.6 mg (69% yield) of a mixture of olefin regioisomers and reduced product (31a:31b:31c = 10:10:1, $^1$H NMR ratio).

Physical state: colorless oil;

$R_f$ = 0.58 (4:1 hexanes/EtOAc);

HRMS ($m/z$): calcd for C$_{14}$H$_{20}$O$_3$SH$^+$[M+H]$^+$, 269.1206; found, 269.1210;

IR (film) $\nu_{\text{max}}$ = 2963, 1598, 1358, 1175, 1097, 958;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.84 – 7.72 (m, 34 H), 7.34 (d, $J$ = 8.0 Hz, 34 H), 5.40 – 5.34 (m, 1 H), 5.29 (q, $J$ = 6.8 Hz, 8 H), 5.16 (q, $J$ = 6.7 Hz, 7 H), 4.95 (dd, $J$ = 10.2, 1.8 Hz, 1 H), 4.88 – 4.82 (m, 1 H), 4.09 – 3.96 (m, 37 H), 2.45 (s, 55 H), 2.39 (t, $J$ = 7.5 Hz, 17 H), 2.34 – 2.27 (m, 16 H), 1.99 – 1.85 (m, 34 H), 1.55 (dt, $J$ = 19.8, 6.5 Hz, 57 H), 1.28 – 1.18 (m, 7 H), 0.90 (dt, $J$ = 11.0, 7.5 Hz, 49 H), 0.79 (dt, $J$ = 11.6, 7.4 Hz, 9 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 144.7, 144.7, 140.9, 136.1, 135.6, 133.4, 129.9, 129.9, 128.0, 128.0, 121.8, 121.4, 116.2, 69.5, 69.3, 69.0, 68.7, 42.0, 36.7, 35.7, 33.5, 32.0, 29.9, 29.8, 27.7, 25.1, 22.8, 21.7, 13.4, 13.2, 12.7, 12.7, 11.5, 10.6.
Compound 2.83: General procedure A was applied, starting with 40 mg (0.109 mmol) of 2.82. The crude mixture was purified by flash chromatography (silica gel, 49:1 hexanes/EtOAc) to provide 19.7 mg (68 % yield) of an unseparable mixture of olefin and reduced product (2.83:2.84 =10:1).

Physical state: colorless oil;

$R_f = 0.58$ (4:1 hexanes/EtOAc);

HRMS ($m/z$): calcd for C$_{14}$H$_{18}$O$_3$SH $[M+H]^+$, 267.1049; found, 267.1048;

IR (film) $\nu_{\text{max}} =$ 2951, 2846, 1597, 1358, 1187, 1174, 1096;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.79 (d, $J = 7.9$ Hz, 2 H), 7.34 (d, $J = 7.8$ Hz, 2 H), 5.35 (s, 1 H), 4.11 (t, $J = 6.9$ Hz, 2 H), 2.45 (s, 3 H), 2.42 (t, $J = 6.2$ Hz, 2 H), 2.26 (bs, 2 H), 2.14 (t, $J = 7.8$ Hz, 2 H), 2.14 – 2.13 (m, 1 H), 1.80 (quintet, $J = 7.8$ Hz, 2 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 144.8, 138.8, 133.3, 129.9, 128.0, 126.7, 69.0, 35.1, 32.6, 30.7, 23.3, 21.8.

Compound 3.9a: The general procedure A was followed starting with 38.1 mg of 5.12 (0.100 mmol). The crude mixture was purified by flash chromatography (silica gel, 49:1 hexanes/EtOAc) to provide 14.2 mg (51% yield) of an unseparable mixture of olefin and
reduced product (3.9a:3.9b = 10:1). For 3.9a, the analytical data was identical to that of literature report.⁶

**Compound 3.10**: The *general procedure A* was followed starting with 1.062 g (2.595 mmol) of 4.13. The crude mixture was purified by flash chromatography (silica gel, 49:1 hexanes/EtOAc) to provide 614.7 mg (74% yield) of 3.10. *For the small scale reaction, the same procedure was followed starting with 49 mg (0.119 mmol) of 4.13 to provide 33.9 mg (92% yield) of 3.10 after chromatography. **For the catalytic reaction, the same procedure was followed starting with 41 mg (0.100 mmol) of 4.13 to provide 15.6 mg (51% yield) of 3.10 after chromatography.**

**Physical state**: white solid;

$R_f = 0.47$ (6:1 hexanes/EtOAc);

$[\alpha]_D = -30.2^\circ$ (c = 0.36, CH$_2$Cl$_2$);

m.p. = 84–86 °C;

HRMS ($m/z$): calcd for C$_{17}$H$_{24}$O$_3$SH$^+ [M+H]$\n^+$, 309.1519; found, 309.1522;

IR (film) $\nu_{\text{max}} = 2925, 1648, 1598, 1452, 1360, 1175, 1097, 921, 872;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.74 (d, $J$ = 7.5 Hz, 2 H), 7.28 (d, $J$ = 7.3 Hz, 2 H), 4.67 (s, 1 H), 4.61 (s, 1 H), 4.46 (td, $J$ = 10.7, 4.0 Hz, 1 H), 2.43 (s, 3 H), 2.24 (d, $J$ = 12.3 Hz, 1 H), 2.12 (t, $J$ = 10.6 Hz, 1 H), 1.65 (t, $J$ = 16.0 Hz, 2 H), 1.52 – 1.46 (m, 1 H), 1.44 (s, 3 H), 1.32 (q, $J$ = 13.2 Hz, 1 H), 1.23 (q, $J$ = 12 Hz, 1 H), 0.92 (d, $J$ = 8.6 Hz, 4 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 145.0, 144.3, 134.8, 129.5, 128.0, 113.1, 83.2, 50.9, 41.9,

---

⁶ Belleau, B.; Gulini, U.; Gour-Salin, B. *Can. J. Chem.* 1985, 63, 1268.
Compound 3.11: General procedure A was applied, starting with 40.7 mg (0.10 mmol) of 5.13. The crude mixture was purified by flash chromatography (silica gel, 19:1 to 9:1 hexanes/EtOAc) followed by pTLC (4:1 hexanes/EtOAc) to provide 3.11 (18.1 mg) in 59% yield.

Physical state: white solid;

R_f = 0.34 (5:1 hexanes/EtOAc);

m.p. = 90–92 °C;

HRMS (m/z): calcd for C_{17}H_{25}NO_{2}S[H]^+, 308.1679; found, 308.1679;

IR (film) ν_max = 3288, 2925, 1449, 1323, 1159, 1093;

^1H NMR (600 MHz, CDCl_3) δ 7.72 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 4.74 (s, 1 H), 4.70 (s, 1 H), 4.34 (bs, 1 H), 2.84 (tt, J = 10.9, 3.8 Hz, 1 H), 2.43 (s, 3 H), 2.31 – 2.26 (m, 1 H), 1.88 – 1.79 (m, 1 H), 1.67 – 1.57 (m, 2 H), 1.46 – 1.35 (m, 1 H), 1.35 – 1.25 (m, 1 H), 1.15 (s, 3 H), 0.97 – 0.89 (m, 2 H), 0.88 (d, J = 6.6 Hz, 3 H);

^13C NMR (151 MHz, CDCl_3) δ 146.1, 143.3, 137.5, 129.6, 127.4, 114.3, 53.6, 52.0, 42.6, 34.0, 31.5, 30.3, 22.1, 21.6, 17.4.

Compound 3.12a, 3.12b: The general procedure B was followed starting with 39.7 mg of 3.17 (0.100 mmol). The crude mixture was purified by flash chromatography (silica gel, 95:5
to 9:1 hexanes/EtOAc) followed by pTLC (5:1 hexanes/EtOAc) to provide 3.12a and 3.12b in 60% yield (17.7 mg) as an inseparable mixture of isomers (3.12a:3.13b = 10:1, NMR ratio).

For 3.12a (major):

**Physical state**: white solid;

$R_f = 0.25$ (4:1 hexanes/Et$_2$O);

**m.p.** = 67–69 ºC;

**HRMS** ($m/z$): calcd for C$_{16}$H$_{25}$NO$_2$SH$^+$$[M+H]^+$, 296.1679; found, 296.1688;

**IR (film)** $\nu_{\text{max}}$ = 3276, 2956, 2869, 1648, 1598, 1448, 1425, 1325, 1159, 1093, 814;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J = 8.3$ Hz, 2 H), 7.29 (d, $J = 7.9$ Hz, 2 H), 4.73 (s, 1 H), 4.62 (s, 1 H), 4.37 (d, $J = 7.2$ Hz, 1 H), 3.34 – 3.27 (m, 1 H), 2.42 (s, 3 H), 2.11 – 1.99 (m, 2 H), 1.63 – 1.56 (m, 1 H), 1.47 (s, 3 H), 1.31 – 1.24 (m, 2 H), 0.83 (d, $J = 6.7$ Hz, 3 H), 0.73 (d, $J = 6.5$ Hz, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 143.4, 141.9, 138.0, 129.7, 127.3, 114.4, 50.2, 44.5, 44.4, 24.5, 22.9, 22.2, 22.0, 21.6.

**Compound 3.13**: A slightly modified general procedure A (2 equiv of TEMPO, 4 equiv of TFA) was applied starting with 38.4 mg (0.096 mmol) of 5.14. The crude mixture was purified by pTLC (2:1 hexanes/Et$_2$O, three elutions) to provide 13.4 mg (47% yield) of 3.13.

**Physical state**: white solid;

$R_f = 0.29$ (2:1 hexanes/Et$_2$O);

$[\alpha]_D = -5.8^\circ$ ($c = 0.41$, CH$_2$Cl$_2$);
m.p. = 64–66 ºC;

HRMS (m/z): calcd for C_{14}H_{19}NO_{4}SH^+ [M+H]^+; 298.1107; found, 298.1099;

IR (film) \nu_{\text{max}} = 3272, 2953, 1743, 1347, 1337, 1161, 1092, 815 \text{ cm}^{-1};

^{1}H NMR (600 MHz, CDCl_3) \delta 7.71 (d, J = 7.8 \text{ Hz}, 2 \text{ H}), 7.29 (d, J = 7.8 \text{ Hz}, 2 \text{ H}), 4.97 (d, J = 8.9 \text{ Hz}, 1 \text{ H}), 4.83 (s, 1 \text{ H}), 4.72 (s, 1 \text{ H}), 4.06 (ddd, J = 8.9, 7.7, 1.3 \text{ Hz}, 1 \text{ H}), 3.49 (s, 3 \text{ H}), 2.46 – 2.31 (m, 5 \text{ H}), 1.64 (s, 3 \text{ H});

^{13}C NMR (151 MHz, CDCl_3) \delta 172.0, 143.8, 139.6, 136.7, 129.7, 127.4, 115.5, 54.3, 52.4, 41.7, 21.9, 21.7.

**Compound 3.14:** A slightly modified general procedure A (2 equiv of TEMPO, 4 equiv of TFA) was applied starting with 42.6 mg (0.100 mmol) of 5.15. The crude mixture was purified by chromatography (silica gel, 2:1 hexanes/Et_2O) and pTLC (2:1 hexanes/Et_2O, two elutions) to provide 14.4 mg (40% yield) of product.

**Physical state:** white solid;

\( R_f = 0.59 \) (1:1 hexanes/Et_2O);

\([\alpha]_D = -5.0^\circ \) (c = 0.1, CH_2Cl_2);

m.p. = 84–86 ºC;

HRMS (m/z): calcd for C_{17}H_{25}NO_{4}SNa^+ [M+Na]^+; 362.1396; found, 362.1401;

IR (film) \nu_{\text{max}} = 2926, 1724, 1599, 1455, 1340, 1152, 1091, 897, 841, 814, 663 \text{ cm}^{-1};

^{1}H NMR (600 MHz, CDCl_3) \delta 7.72 (d, J = 8.2 \text{ Hz}, 2 \text{ H}), 7.27 (d, J = 8.2 \text{ Hz}, 2 \text{ H}), 5.03 (d, J = 8.9 \text{ Hz}, 1 \text{ H}), 4.83 (s, 1 \text{ H}), 4.74 (s, 1 \text{ H}), 3.93 (ddd, J = 8.9, 7.6, 6.5 \text{ Hz}, 1 \text{ H}), 2.43 – 2.36 (m, 4 \text{ H}), 2.32 (dd, J = 13.9, 7.6 \text{ Hz}, 1 \text{ H}), 1.70 (s, 3 \text{ H}), 1.24 (s, 9 \text{ H});

^{13}C NMR (151 MHz, CDCl_3) \delta 170.6, 143.6, 140.0, 137.0, 129.7, 127.4, 115.2, 82.6, 54.7,
42.2, 27.8, 22.0, 21.6.

**Compound 3.15a:** A slightly modified *general procedure A* (2 equiv of TEMPO, 4 equiv of TFA) was applied starting with 38.4 mg (0.100 mmol) of 5.16. The crude mixture was purified by pTLC (5:1 hexanes/EtOAc, two elutions) to provide 16.2 mg (51% yield) of an inseparable mixture of olefin and reduction products (3.15a:3.15b = 7:1, NMR ratio).

**Physical state:** white solid;

$R_f = 0.22$ (5:1 hexanes/EtOAc);

$[\alpha]_D = +17.6^\circ$ (c =1.6, CHCl$_3$);

m.p. = 68–71 ºC;

**HRMS (m/z):** calcd for C$_{13}$H$_{17}$NO$_4$SH$^+ [M+H]^+$, 284.0951; found, 284.0949;

**IR (film)** $\nu_{\text{max}} = 2923, 2853, 1738, 1436, 1335, 1160, 1090, 1019, 880, 815, 663$ cm$^{-1}$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.72 (d, $J = 8.3$ Hz, 2 H), 7.28 (d, $J = 8.0$ Hz, 2 H), 5.33 (d, $J = 7.9$ Hz, 1 H), 4.97 (d, $J = 10.2$ Hz, 2 H), 4.43 (d, $J = 8.0$ Hz, 1 H), 3.58 (s, 3 H), 2.42 (s, 3 H), 1.64 (s, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 170.4, 143.8, 139.3, 136.9, 129.7, 127.4, 116.3, 61.1, 53.0, 21.7, 18.8.

**Compound (–)-3.16:** The *general procedure B* was followed starting with 38.1 mg (0.100 mmol) of (–)-3.21. The crude mixture was purified by flash
chromatography (silica gel, 1:0 to 9:1 hexanes/EtOAc) followed by pTLC (5:1 hexanes/EtOAc) to provide (−)-3.16 (14.0 mg) in 50% yield.

**Physical state**: white solid;

$R_f = 0.36$ (4:1 hexanes/EtOAc);

$[\alpha]_D = -1.6^\circ$ ($c = 0.24$, CH$_2$Cl$_2$);

m.p. = 82–84 °C;

**HRMS (m/z)**: calcd for C$_{15}$H$_{21}$NO$_2$SNa$^+$ [M+H]$^+$, 302.1185; found, 302.1191;

**IR (film)** $\nu_{\text{max}} = 3272, 2926, 1434, 1320, 1156, 1079$;

**$^1$H NMR (600 MHz, CDCl$_3$)** $\delta$ 7.70 (d, $J = 8.4$ Hz, 2 H), 7.27 (d, $J = 7.8$ Hz, 2 H), 5.45 (s, 1 H), 4.32 (d, $J = 7.4$ Hz, 1 H), 3.83 (quintet, $J = 7.0$ Hz, 1 H), 2.42 (s, 3 H), 1.87 – 1.71 (m, 3 H), 1.65 – 1.56 (m, 1 H), 1.50 – 1.41 (m, 1 H), 1.40 – 1.32 (m, 2 H), 1.28 – 1.18 (m, 1 H), 1.16 (d, $J = 6.9$ Hz, 3 H);

**$^{13}$C NMR (151 MHz, CDCl$_3$)** $\delta$ 143.1, 138.2, 136.9, 129.4, 127.4, 124.1, 55.6, 24.9, 23.7, 22.3, 22.2, 21.6, 20.6.

Compounds 3.28a, 3.28b: The general procedure A was followed starting with 38.0 mg (0.079 mmol) of 3.27. The crude mixture was purified by flash chromatography (silica gel, 1:0 to 79:1 hexanes/EtOAc) to provide 13.7 mg (46% yield) of a mixture of olefin regioisomers (3.28a:3.28b = 2:1, NMR ratio). Product 3.28a was observed to crystallize out
of the mixture, however any attempts to isolate the minor isomer 3.28b by pTLC were unsuccessful.

For 3.28a:

Physical state: white solid;

$R_f = 0.6$ (6:1 hexanes/EtOAc);

$[\alpha]_D = +24.5^\circ (c = 0.11, \text{CH}_2\text{Cl}_2)$;

m.p. = 106–108 °C;

HRMS ($m/z$): calcd for C$_{22}$H$_{32}$O$_3$SH$^+$ [M+H]$^+$, 377.2145; found, 377.2158;

IR (film) $\nu_{\text{max}} = 2925, 1454, 1343, 1174, 909$;

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.71 (d, $J = 7.4$ Hz, 2 H), 7.24 (d, $J = 7.6$ Hz, 2 H), 5.03 (t, $J = 10.6$ Hz, 1 H), 4.58 (s, 1 H), 4.48 (s, 1 H), 2.42 (s, 3 H), 2.22 (t, $J = 9.4$ Hz, 1 H), 2.14 (bs, 1 H), 1.72 – 1.63 (m, 5 H), 1.61 – 1.54 (m, 1 H), 1.51 – 1.35 (m, 5 H), 1.24 (d, $J = 12.1$ Hz, 1 H), 1.19 – 1.06 (m, 2 H), 1.01 (d, $J = 7.2$ Hz, 3 H), 0.97 (s, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) δ 145.4, 143.6, 136.0, 129.1, 127.5, 114.0, 85.8, 54.1, 52.0, 43.5, 42.1, 36.2, 33.2, 27.3, 26.8, 21.7, 20.7, 19.3, 17.0, 14.9.

For the mixture:

IR (film) $\nu_{\text{max}} = 2925, 1454, 1343, 1173, 906$;

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.71 (d, $J = 8.3$ Hz, 8 H), 7.68 (d, $J = 8.3$ Hz, 2 H), 7.24 (d, $J = 8.1$ Hz, 10 H), 5.03 (t, $J = 10.7$ Hz, 4 H), 4.92 (t, $J = 10.7$ Hz, 1 H), 4.69 (s, 1 H), 4.67 (s, 1 H), 4.58 (s, 4 H), 4.48 (s, 4 H), 2.41 (s, 12 H), 2.40 (s, 3 H), 2.28 (d, $J = 10.8$ Hz, 1 H), 2.26 – 2.17 (m, 5 H), 2.17 – 2.10 (m, 5 H), 1.82 (td, $J = 12.8$, 5.4 Hz, 1 H), 1.75 (ddd, $J = 9.6$, 7.1, 3.3 Hz, 1 H), 1.72 – 1.67 (m, 3 H), 1.63 (dd, $J = 13.5$, 3.6 Hz, 3 H), 1.60 – 1.54 (m, 11 H), 1.52 – 1.35 (m, 24 H), 1.35 – 1.21 (m, 10 H), 1.13 (dtd, $J = 29.8$, 13.1, 3.2 Hz, 9 H), 1.02 (t, $J$
\text{H} = 8.9 \text{ Hz}, 13 \text{ H}), 0.96 (s, 12 \text{ H}), 0.88 (dt, J = 14.7, 7.3 \text{ Hz}, 6 \text{ H});

\text{\textsuperscript{13}C NMR (151 MHz, CDCl} \text{3}) \, \delta \, 145.3, 145.0, 143.6, 143.4, 136.6, 136.0, 129.1, 129.1, 127.5, 127.1, 114.0, 108.2, 86.5, 85.8, 55.5, 54.1, 51.9, 49.0, 43.5, 42.1, 39.9, 39.3, 37.9, 36.2, 33.2, 27.3, 26.8, 26.0, 24.3, 21.71, 21.7, 21.2, 20.7, 19.3, 18.5, 17.6, 17.0, 15.6, 14.9.

\text{Compounds 3.30 and 3.31: The general procedure B was followed (reaction run at 4 \text{ ºC})! starting with 53.8 mg (0.100 mmol) of 3.29. The crude mixture was purified by flash chromatography (silica gel, 5:1 hexanes/EtOAc) and pTLC (5:1 hexanes/EtOAc) to provide 13.3 mg of 3.30 (30\% yield) and 5.4 mg of 3.31 (16\% yield). For 3.30:}

\text{Physical state: white solid;}
\text{\textit{R}f} = 0.18 (10:1 hexanes/Et}_2\text{O);}
\text{\textit{[\alpha]D} = +122.9 \text{ \degree} (c = 0.45, CH}_2\text{Cl}_2);}
\text{m.p.} = 124–126 \text{ ºC;}
\text{HRMS (\textit{m/z})}: \text{calcd for C}_{27}\text{H}_{35}\text{NO}_2\text{SH}^+ \text{[M+H]}^+, 438.2461; \text{found, 438.2458;}
\text{IR (film) \textit{v}_{max} = 2956, 2871, 1613, 1458, 1337, 1156, 1103, 1045 cm}^{-1};
\text{\textsuperscript{1}H NMR (600 MHz, CDCl} \text{3}) \, \delta \, 7.74 (d, J = 8.2 \text{ Hz}, 1 \text{ H}), 7.06 (dd, J = 8.2, 2.0 \text{ Hz}, 1 \text{ H}), 6.86 (d, J = 8.2 \text{ Hz}, 2 \text{ H}), 6.81 (d, J = 8.2 \text{ Hz}, 2 \text{ H}), 6.60 (d, J = 2.0 \text{ Hz}, 1 \text{ H}), 3.75 (d, J = 9.3 \text{ Hz}, 1 \text{ H}), 3.34 (d, J = 9.3 \text{ Hz}, 1 \text{ H}), 2.90 – 2.79 (m, 2 \text{ H}), 2.57 (ddd, J = 18.4, 11.9, 7.1 \text{ Hz}, 1 \text{ H}), 2.27 (s, 3 \text{ H}), 2.19 – 2.09 (m, 1 \text{ H}), 2.06 (dd, J = 17.5, 6.6 \text{ Hz}, 1 \text{ H}), 1.84 – 1.75 (m, 2 \text{ H}),
1.67 – 1.56 (m, 1 H), 1.37 – 1.28 (m, 2 H), 1.28 – 1.18 (m, 7 H), 0.92 (s, 3 H), 0.79 (s, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 148.3, 141.3, 139.0, 136.6, 131.6, 129.2, 128.5, 126.2, 126.0, 123.5, 69.7, 58.6, 45.7, 41.0, 33.7, 33.4, 30.7, 26.0, 25.7, 24.2, 24.0, 21.4, 18.9, 18.5, 13.1.

For 3.31:

**Physical state**: white solid;

$R_f$ = 0.21 (10:1 hexanes/Et$_2$O);

$[\alpha]_D^\circ = +48.1$° ($c$ = 0.21, CH$_2$Cl$_2$);

m.p. = 162–164°C;

HRMS (m/z): calcd for C$_{27}$H$_{35}$NO$_2$SH$^+$ [M+H]$^+$, 438.2461; found, 438.2469;

IR (film) $\nu_{max}$ = 3279, 2959, 1461, 1326, 1160, 1094 cm$^{-1}$;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J$ = 8.2 Hz, 2 H), 7.27 (d, $J$ = 8.2 Hz, 2 H), 7.15 (d, $J$ = 8.1 Hz, 1H), 7.02 (dd, $J$ = 8.1, 1.4 Hz, 1 H), 6.87 (s, 1 H), 5.90 (ddd, $J$ = 10.0, 6.3, 1.7 Hz, 1 H), 5.21 (dd, $J$ = 10.0, 2.8 Hz, 1 H), 4.28 (dd, $J$ = 10.0, 2.2 Hz, 1 H), 3.07 (dd, $J$ = 12.0, 10.2 Hz, 1 H), 2.84 (heptet, $J$ = 7.0 Hz, 1 H), 2.78 (dt, $J$ = 17.0, 3.0 Hz, 1 H), 2.72 – 2.63 (m, 1 H), 2.53 (dd, $J$ = 17.0, 6.3 Hz, 1 H), 2.46 (dd, $J$ = 12.3, 2.7 Hz, 1 H), 2.42 (s, 3 H), 2.10 (d, $J$ = 17.9 Hz, 1 H), 2.05 – 1.99 (m, 1 H), 1.66 – 1.61 (m, 2 H), 1.27 – 1.20 (m, 9 H), 0.92 (s, 3 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 145.9, 144.5, 143.3, 137.3, 135.3, 132.6, 129.8, 128.9, 127.1, 126.8, 125.8, 124.3, 51.2, 40.9, 39.6, 39.4, 36.5, 33.6, 30.7, 25.5, 24.1, 24.1, 21.6, 19.8, 19.7.
Compound 3.33a: The general procedure A was followed starting with 25 mg (0.036 mmol) of 3.32. The crude mixture was purified by flash chromatography (silica gel, 1:0 to 49:1 DCM/Et₂O) and pTLC (1:1 hexanes/Et₂O) to provide 10.1 mg (47% yield) of a mixture of product and traces of reduced byproduct (3.33a:3.33b = 10:1, ¹H NMR ratio).

Physical state: white solid;

Rf = 0.18 (4:1 hexanes/EtOAc);

[α]D = +55.5 ° (c = 0.29, CH₂Cl₂);

m.p. = 174–176 °C;

HRMS (m/z): calcd for C₃₇H₅₄O₄S⁺ [M+H]⁺, 595.3815; found, 595.3811;

IR (film) νmax = 2927, 1457, 1356, 1174, 956 cm⁻¹;

¹H NMR (600 MHz, CDCl₃) δ 7.80 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.1 Hz, 2 H), 6.26 (dd, J = 10.6, 2.9 Hz, 1 H), 5.54 (d, J = 10.4 Hz, 1 H), 3.72 (s, 2 H), 3.24 (dd, J = 11.5, 4.6 Hz, 1 H), 2.45 (s, 4 H), 2.34 (dd, J = 14.2, 1.7 Hz, 1 H), 1.91 – 1.85 (m, 2 H), 1.75 (d, J = 14.4 Hz, 1 H), 1.72 – 1.50 (m, 7 H), 1.45 – 1.28 (m, 8 H), 1.19 – 1.13 (m, 1 H), 1.01 (s, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H), 0.88 (s, 3 H), 0.77 (s, 3 H), 0.75 (s, 3 H), 0.68 (s, 3 H);

¹³C NMR (151 MHz, CDCl₃) δ 144.7, 135.4, 134.9, 133.2, 129.9, 128.0, 126.3, 125.4, 80.1, 79.1, 54.9, 54.3, 42.6, 40.4, 39.0, 38.1, 37.6, 37.0, 36.7, 36.0, 34.9, 32.4, 32.1, 29.6, 27.9, 27.2, 25.3, 24.4, 21.8, 20.3, 19.3, 18.4, 18.1, 16.6, 15.1.
Compound 3.35: A 5 mL vial, flame dried and maintained under Ar was charged with 3.34 (21 mg, 0.030 mmol, 1 equiv) and TEMPO (9.4 mg, 0.060 mmol, 2 equiv). Next, previously degassed CH$_3$NO$_2$ (1.2 mL) was added and only TEMPO was observed to go into solution. Upon addition of TFA (13.7 mg, 9.2 µL, 0.12 mmol, 4 equiv) and sonication of the reaction mixture (2–3 min) a cloudy suspension was obtained. The vial was then immersed in a preheated oil bath at 60 ºC and the reaction proceeded for 1.5 h (LC-MS control). During this time, a white solid was observed to precipitate out of the solution. After the allotted reaction time (1.5 h), the crude mixture was centrifuged to separate a white solid which was then washed with CH$_3$NO$_2$ (1 mL). The resulting solid residue was taken up in CH$_2$Cl$_2$ and purified by chromatography (silica gel, 20:1 CH$_2$Cl$_2$/MeOH) to obtain 6.2 mg (35% yield) of 3.35. (No desired product was detected in the remaining crude reaction solution.)

Physical state: white solid;

$R_f = 0.44$ (10:1 CH$_2$Cl$_2$/MeOH);

$[\alpha]_D = -12.6$ º ($c = 0.6$, CHCl$_3$);

m.p. = 264–267 ºC;

HRMS (m/z): calcd for C$_{30}$H$_{41}$N$_5$O$_8$SH$^+$ [M+H]$^+$, 600.2857; found, 600.2857;

IR (film) $\nu_{\text{max}}$=3263, 1628, 1537, 1161;

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.12 (d, $J = 7.0$ Hz, 1 H), 7.85 (d, $J = 8.6$ Hz, 1 H), 7.82 (d, $J = 9.4$ Hz, 1 H) 7.62 (d, $J = 8.2$ Hz, 2 H), 7.53 (d, $J = 8.5$ Hz, 1 H), 7.31 (d, $J = 8.2$ Hz, 2
H), 7.25 – 7.12 (m, 6 H), 7.04 (bs, 1 H), 4.67 (bs, 2 H), 4.44 (td, J = 8.5, 5.2 Hz, 1 H), 4.07 – 3.96 (m, 2 H), 3.92 (td, J = 9.3, 5.3 Hz, 1 H), 2.97 (dd, J = 13.9, 5.1 Hz, 1 H), 2.78 (dd, J = 13.9, 9.0 Hz, 1 H), 2.36 (s, 3 H), 2.15 (dd, J = 14.1, 5.4 Hz, 1 H), 2.06 (dd, J = 14.1, 9.6 Hz, 1 H), 1.91 – 1.81 (m, 1 H), 1.57 (s, 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.71 (d, J = 6.7 Hz, 3 H), 0.70 (d, J = 6.8 Hz, 3 H);

^{13}C\ \text{NMR (151 MHz, DMSO-}d_{6})\ \delta\ 172.7,\ 171.6,\ 170.4,\ 170.2,\ 142.3,\ 140.5,\ 138.3,\ 137.8,\ 129.1,\ 129.1,\ 128.0,\ 126.7,\ 126.2,\ 113.8,\ 57.7,\ 54.3,\ 53.5,\ 47.9,\ 40.8,\ 37.6,\ 30.5,\ 21.7,\ 21.0,\ 19.1,\ 17.9,\ 17.6.

Section 4. Mechanistic studies

\[\text{Compound 5.17: 1. A flame dried round bottom flask, was kept under Ar and charged with}\]
cyclopentane-carboxylic acid (1g, 8.76 mmol, 1 equiv) which was dissolved in dry THF (8.8 mL) and the resulting solution was cooled at –78 °C. To this, a solution of secBuLi (1.1 M in cyclohexane, 23.9 mL, 26.28 mmol, 3 equiv) was added dropwise and the reaction was maintained at –78 °C for 10 min, before being transferred in an ice bath (0 °C) and stirred for 1h. After this time, D\textsubscript{2}O (1.75 g, 1.75 mL, 87.6 mmol, 10 equiv) was added dropwise and the resulting mixture was kept at 0 °C for another hour before being quenched with 1N HCl (5 mL). After separation of the aqueous layer, the organic solution was further washed with water (2 x 5 mL) and then shaken with 3N KOH (10 mL, until pH ≈ 12). After portioning of
the layers, the resulting aqueous solution was acidified with 3N HCl (15 mL, until pH ≈ 1) and the product was extracted with Et₂O (3 x 30 mL). The resulting organic solution was washed with brine (20 mL), dried over MgSO₄, filtered and concentrated in vacuo to give the desired deuterated acid (672 mg, 67% yield) which was used without further purification.

2. A flame dried 20 mL vial was charged with LAH (332.4 mg, 5.2 mmol, 3 equiv) in THF (5 mL). To this slurry, a solution of the previously prepared α,α-bisdeuterated cyclopentane-carboxylic acid (119.2 mg, 1.731 mmol, 1 equiv) in THF (3 mL + 2 mL rinse) was added dropwise at 0 ºC. The resulting reaction mixture was allowed to proceed under Ar, at room temperature for 2 h before being quenched with H₂O (0.3 mL), 1N KOH (0.6 mL) and H₂O (0.9 mL). To this white slurry, Et₂O (5 mL) was added and after separation of the organic layer, the aqueous mixture was further extracted with Et₂O (3 x 5 mL). The combined organic solution was then washed with brine (20 mL), dried over MgSO₄, filtered and concentrated in vacuo (from ice) to give the desired alcohol in 93% yield (162.4 mg).

3. A flame dried 20 mL vial was charged with the previously prepared alcohol (162.4 mg, 1.606 mmol, 1 equiv) which was dissolved in DCM (7 mL) and cooled at 0 ºC. To this solution, MsCl (220 mg, 1.927 mmol, 1.2 equiv) was added followed by NEt₃ (324.4 mg, 0.43 mL, 3.212 mmol, 2 equiv). The resulting reaction mixture was stirred under Ar for 20 min at 0 ºC, then at room temperature for 40 min before being quenched with saturated NH₄Cl (4 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude mixture was further purified by chromatography (silica gel, 10:1 hexanes/ EtOAc) to give the desired mesylate 5.17 in 67% (192.7 mg).

**Physical state:** colorless oil;
$R_f = 0.28$ (4:1 hexanes/EtOAc);

**HRMS ($m/z$):** calcd for C$_7$H$_{13}$DO$_3$SNa$^+ [M+Na]^+$, 202.0618; found, 202.0620;

**IR (film) $\nu_{\text{max}}$** = 2951, 1350, 1172, 944;

**$^1$H NMR (600 MHz, CDCl$_3$) $\delta$** 4.11 (s, 2 H), 3.00 (s, 3 H), 1.83 – 1.76 (m, 2 H), 1.68 – 1.56 (m, 4 H), 1.34 – 1.21 (m, 2 H);

**$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$** 73.8, 38.6 – 38.3 (m), 37.4, 29.0, 25.4.

---

**Compound 5.18:** 1. A flame dried 20 mL vial was charged with 5.17 (148.5 mg, 0.829 mmol, 1 equiv) and NaCN (203 mg, 4.145 mmol, 5 equiv) and then DMSO (4.2 mL) was added to produce a cloudy suspension. This mixture was stirred at 60 ºC for 5h (TLC control) and it was then diluted with H$_2$O (10 mL) and extracted with Et$_2$O (5 x 3 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The resulting mixture was filtered through a plug of silica (to remove traces of DMSO) (elute with Et$_2$O) and the resulting solution was concentrated *in vacuo* and used in the next reaction as such.

2. The previously prepared nitrile was transferred to a flame dried vial, kept under Ar, dissolved in DCM (8.3 mL) and the solution was cooled at –78 ºC. To this, DIBAL-H (1M in hexanes, 1.650 mmol, 2 equiv) was added dropwise and the resulting reaction mixture was stirred at the same temperature (-78 ºC) for 1.5h. Acetone (1 mL) was then added before the mixture was warmed up to room temperature. The crude mixture was dissolved in Et$_2$O (15
mL) and a solution of Rochelle salt (15 mL) was added and the resulting slurry was vigorously stirred overnight at room temperature. After the layers were partitioned, the aqueous solution was further extracted with Et₂O (5 x 5 mL) and the combined organic layers were washed with brine (20 mL), dried over MgSO₄, filtered and concentrated *in vacuo* (from ice!). The resulting mixture was used in the next reaction without purification.

3. The previously synthesized aldehyde was placed in a 20 mL flame dried vial, kept under Ar and dissolved in THF (8 mL). This solution was cooled at 0 °C and LAH (4 M in Et₂O, 2.440 mmol, 0.6 mL, 3 equiv) was added dropwise. The resulting white slurry was stirred at room temperature overnight before being quenched with H₂O (0.2 mL), 1M KOH (0.4 mL) and H₂O (0.6 mL). After the layers were partitioned, the aqueous solution was further extracted with Et₂O (3 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The desired product 5.18 was isolated after chromatography (silica gel, 10:1 hexanes/EtOAc) in 20% yield (over three steps) (19.1 mg).

**Physical state**: colorless oil;

\[ R_f = 0.33 \text{ (4:1 hexanes/EtOAc);} \]

**IR (film) \( \nu_{\text{max}} \)**: 3316, 2945, 2859, 1451, 1048;

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\text{)} \delta 3.66 (t, J = 6.9 \text{ Hz, 2 H}), 1.80 - 1.72 (m, 2 H), 1.65 - 1.56 (m, 4 H), 1.56 - 1.46 (m, 2 H), 1.29 (bs, 1H), 1.15 - 1.05 (m, 2 H); \]

\[ ^13C \text{ NMR (151 MHz, CDCl}_3\text{)} \delta 62.6, 39.1, 36.4 - 36.0 (m), 32.7, 25.2. \]
**Compound 4.1:** The product was obtained following the *general procedure* for the installation of the directing group (*vide supra*) starting with 6.2 mg (0.053 mmol) of 5.18. After purification by flash chromatography (silica gel, 10:1 hexanes/EtOAc), 4.1 was obtained in 63 % yield (12.5 mg).

**Physical state:** yellow oil;

*R* = 0.45 (4:1 hexanes/EtOAc);

**HRMS (m/z):** calcd for C_{18}H_{28}D_{3}N_{2}O_{3}SH^{+} [M+H]^+ , 369.2064; found, 369.2061;

**IR (film) ν_{max} =** 2936, 1593, 1388, 1349, 1174;

**$^1$H NMR (600 MHz, CDCl$_3$) δ 7.84 (d, *J* = 8.1 Hz, 1 H), 7.37 (s, 1 H), 6.99 (d, *J* = 8.0 Hz, 1 H), 4.03 (t, *J* = 6.7 Hz, 2 H), 3.83 (q, *J* = 6.8 Hz, 4 H), 2.39 (s, 3 H), 1.68 – 1.60 (m, 4 H), 1.60 – 1.50 (m, 2 H), 1.50 – 1.41 (m, 2 H), 1.36 (t, *J* = 7.1 Hz, 3 H), 1.27 (t, *J* = 5.8 Hz, 3 H), 1.02 – 0.94 (m, 2H);

**$^{13}$C NMR (151 MHz, CDCl$_3$) δ 149.3, 145.1, 130.6, 126.1, 125.1, 118.4, 69.9, 49.4, 42.4, 36.07 – 35.61 (m), 35.0, 32.3, 25.1, 21.8, 14.6, 11.4.

**Compound 4.2:** The *general procedure* A was followed starting with 7.6 mg of 4.1 (0.028 mmol). After the allotted reaction time (1.5h), the crude reaction was cooled at room temperature and the solvent was removed *in vacuo*. The resulting crude mixture was dissolved in a solution of CDCl$_3$ (0.5 mL) containing trimethoxybenzene (3.14 mg/mL; 0.056 mmol/mL) as an internal standard and analyzed by $^1$H NMR to obtain a product yield (34%)
corresponding to a 8:1 mixture of 4.2:4.3.

**Physical state**: colorless oil;

$R_f = 0.53$ (4:1 hexanes/EtOAc);

**HRMS (m/z)**: calcd for C$_{14}$H$_{17}$DO$_3$SH$^+$/[M+H]$^+$, 268.1111; found, 268.1120;

**IR (film)** $v_{max} = 2924, 1594, 1359, 1180, 966$;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.82 – 7.76 (m, 1 H), 7.38 – 7.32 (m, 2 H), 5.38 – 5.31 (m, 1 H), 4.12 (t, $J = 6.9$ Hz, 2 H), 2.45 (s, 3 H), 2.41 (t, $J = 7.2$ Hz, 2 H), 2.29 – 2.22 (m, 2 H), 2.14 (t, $J = 8$ Hz, 2 H), 1.79 (quintet, $J = 8$ Hz, 2 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 144.8, 138.7, 133.2, 129.8 (d, $J = 17.2$ Hz), 128.0, 126.6, 68.9, 35.1, 32.6, 30.7, 23.3, 21.8.

![Reaction Scheme]

**Compound 4.4**: 1. A 10 mL vial was flame dried and charged with methyl 2-cyclopentylacetate (100 mg, 0.675 mmol, 1 equiv) and dissolved in a freshly prepared solution of Na in CD$_3$OD (0.33 M, 2 mL, 2 equiv). The resulting mixture was stirred at 60 °C for 48h. After this time, the solution was concentrated in vacuo and then the crude mixture was dissolved in EtOAc (5 mL) and washed with saturated NH$_4$Cl (5 mL). Upon separation of the organic layer, the aqueous solution was further extracted with EtOAc (3 x 5 mL) and the combined organic fractions were washed with brine (10 mL), dried over MgSO$_4$, filtered and concentrated in vacuo. This crude mixture was flushed through a silica gel plug (elute
with DCM) to give the desired product (40 mg, 42% yield) which was used in the next reaction without further purification.

2. The previously prepared deuterated ester (40 mg, 0.281 mmol, 1 equiv) was transferred in a flame-dried vial and dissolved in THF (1 mL). To this, LAH (0.5M solution in Et₂O, 2 mL, 3.66 equiv) was added dropwise and the resulting solution was stirred at reflux for 4h, before being quenched with H₂O (1 mL), 1N NaOH (2 mL) and H₂O (3 mL). This heterogenous solution was then filtered through celite (elute with DCM), concentrated in vacuo and the crude mixture was purified by chromatography (silica gel, 1:1 to 1:3 hexanes/DCM) to give the desired alcohol (14 mg, 44% yield).

3. The product was obtained following the general procedure for the installation of the directing group (vide supra) starting with 10.7 mg (0.092 mmol) of the previously prepared alcohol. After purification by flash chromatography (silica gel, 10:1 hexanes/EtOAc), 4.4 was obtained in 90% yield (30.3 mg).

**Physical state**: yellow oil;

R_f = 0.58 (4:1 hexanes/EtOAc);

**HRMS (m/z)**: calcd for C_{18}H_{27}D_{2}N_{3}SH\(^{+}\) [M+H]\(^{+}\), 370.2126; found, 370.2127;

**IR (film)** \(\nu_{max}\) = 2939, 1593, 1389, 1350, 1174;

**\(^1\)H NMR (400 MHz, CDCl\(_3\))** \(\delta\) 7.85 (d, \(J = 8.1\) Hz, 1 H), 7.37 (s, 1 H), 7.00 (d, \(J = 8.0\) Hz, 1 H), 4.03 (s, 2 H), 3.83 (q, \(J = 6.7\) Hz, 4 H), 2.39 (s, 3 H), 1.80 (quintet, \(J = 5.6\) Hz, 1 H), 1.70 – 1.62 (m, 2 H), 1.60 – 1.51 (m, 2 H), 1.49 – 1.41 (m, 2 H), 1.36 (t, \(J = 7.1\) Hz, 3 H), 1.27 (t, \(J = 8.9\) Hz, 3 H), 1.05 – 0.96 (m, 2 H);

**\(^{13}\)C NMR (151 MHz, CDCl\(_3\))** \(\delta\) 149.3, 145.1, 130.6, 126.1, 125.1, 118.4, 69.8, 49.4, 42.4, 36.1, 34.6 – 34.2 (m), 32.4, 25.0, 21.8, 14.6, 11.4.
Compound 4.5: The general procedure A was followed starting with 5.3 mg of 4.4 (0.014 mmol). After the allotted reaction time (1.5h), the crude reaction was cooled at rt and the solvent was removed in vacuo. The resulting crude mixture was dissolved in a solution of CDCl₃ (0.5 mL) containing trimethoxybenzene (1.6 mg/mL; 0.0095 mmol/mL) as an internal standard and analyzed by ¹H NMR to obtain a product yield (58%).

Physical state: colorless oil;

$R_f = 0.51$ (4:1 hexanes/EtOAc);

HRMS ($m/z$): calcd for C₁₄H₁₆D₂O₃SH⁺ [M+H]⁺, 269.1173; found, 269.1180;

IR (film) $ν_{max} = 2951, 2846, 1357, 1175, 976;

¹H NMR (400 MHz, CDCl₃) $δ$ 7.79 (d, $J = 7.1$ Hz, 2 H), 7.34 (d, $J = 8.1$ Hz, 2 H), 5.41 – 5.29 (m, 1 H), 4.10 (s, 2 H), 2.45 (s, 3 H), 2.27 – 2.23 (m, 2 H), 2.16 – 2.11 (m, 2 H), 1.80 (quintet, $J = 5.2$ Hz, 2 H);

¹³C NMR (151 MHz, CDCl₃) $δ$ 144.8, 138.6, 133.3, 129.9, 128.0, 126.7, 68.9, 35.0, 32.6, 30.0 – 29.9 (m), 23.3, 21.8.

**Compound 4.6:** 1. In a 20 mL vial, flame dried and kept under Ar, a solution of 2-cyclopentylacetyl chloride (300 mg, 2.046 mmol, 1 equiv) in THF (10 mL) was treated with a solution of LiAlD₄ (1 M in Et₂O, 5.100 mmol, 2.5 equiv) which was added dropwise. The resulting white slurry was stirred at room temperature for 2 h, before being carefully
quenched with H$_2$O (0.3 mL), 1 M KOH (0.6 mL) and H$_2$O (0.9 mL). The product was 
extracted from the mixture with EtOAc (3 x 5 mL) and the resulting organic solution was 
washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo to give 229.4 mg of 
alcohol which was used without further purification.

2. The product was obtained following the general procedure for the installation of the 
directing group (vide supra) starting with 12 mg (0.103 mmol) of the previously prepared 
alcohol. After purification by flash chromatography (silica gel, 10:1 hexanes/EtOAc), 4.1 
was obtained in 97% yield (36.8 mg).

**Physical state:** yellow oil;

$R_f$ = 0.49 (4:1 hexanes/EtOAc);

**HRMS (m/z):** calcd for C$_{18}$H$_{27}$D$_2$N$_3$O$_3$SH$^+$ [M+H]$^+$, 370.2126; found, 370.2130;

**IR (film) $\nu_{\text{max}}$** = 2937, 1711, 1465, 1452, 1180, 1142, 963;

**$^1$H NMR (400 MHz, CDCl$_3$)** $\delta$ 7.84 (d, $J$ = 8.1 Hz, 1 H), 7.36 (s, 1 H), 6.99 (d, $J$ = 8.1 Hz, 1 H), 3.82 (q, $J$ = 7.2 Hz, 4 H), 2.39 (s, 3 H), 1.81 (heptet, $J$ = 14.9 Hz, 1 H), 1.71 – 1.58 (m, 4 H), 1.58 – 1.50 (m, 2 H), 1.50 – 1.40 (m, 2 H), 1.35 (t, $J$ = 7.2 Hz, 3 H), 1.27 (t, $J$ = 7.2 Hz, 3 H), 1.04 – 0.93 (m, 2 H);

**$^{13}$C NMR (101 MHz, CDCl$_3$)** $\delta$ 149.3, 145.1, 130.6, 126.2, 125.1, 118.4, 69.65 – 68.94 (m), 49.4, 42.4, 36.2, 34.9, 32.4, 25.0, 21.8, 14.6, 11.4.

**Compound 4.7:** The general procedure A was followed starting with 11.4 mg (0.030 mmol) of 4.6. After the allotted reaction time (1.5h), the crude reaction was cooled to room temperature and the solvent was removed in vacuo. The resulting crude mixture was dissolved in a solution of CDCl$_3$ (1 mL) containing
trimethoxybenzene (1.68 mg/mL; 0.010 mmol/mL) as an internal standard and analyzed by 

$^1$H NMR to obtain a product yield (53%).

**Physical state:** colorless oil;

$R_f = 0.53$ (4:1 hexanes/EtOAc);

**HRMS (m/z):** calcd for C$_{14}$H$_{16}$D$_2$O$_3$SH$^+ [M+H]$^+$, 269.1173; found, 269.1184;

**IR (film) $\nu_{\text{max}}$ = 2925, 2846, 1597, 1359, 1176, 958;**

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.79 (t, $J = 7.0$ Hz, 2 H), 7.34 (d, $J = 8.0$ Hz, 2 H), 5.35 (s, 1 H), 2.45 (s, 3 H), 2.40 (s, 2 H), 2.29 – 2.22 (m, 2 H), 2.14 (t, $J = 6.5$ Hz, 2 H), 1.80 (quintet, $J = 7.2$ Hz, 2 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 144.8, 138.7, 133.3, 129.9, 128.0, 126.6, 68.3 – 68.2 (m), 35.1, 32.6, 30.4, 23.3, 21.8.

**Compound 4.8:** Synthesized from 5-methylhex-1-yn-3-ol (0.300 mmol) following the general procedure. After purification on silica gel (10:1 hexanes/EtOAc), the product was obtained in 86% yield (94.7 mg).

**Physical state:** pale orange oil;

$R_f = 0.50$ (5:1 hexanes/EtOAc);

**HRMS (m/z):** calcd for C$_{18}$H$_{27}$N$_3$O$_3$SH$^+ [M+H]$^+$, 366.1884; found, 366.1883;

**IR (film) $\nu_{\text{max}}$ = 2959, 1593, 1466, 1389, 1353, 1271, 1175, 1110, 923, 882, 675;**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.86 (d, $J = 8.1$ Hz, 1 H), 7.37 (s, 1 H), 6.98 (d, $J = 8.1$ Hz, 1 H), 5.11 (dt, $J = 2.1$, 7.1 Hz, 1 H), 3.92 – 3.75 (m, 4 H), 2.39 (s, 3 H), 2.35 (d, $J = 2.1$ Hz, 1 H), 1.86 – 1.72 (m, 2 H), 1.66 – 1.60 (m, 1 H), 1.35 (t, $J = 7.1$ Hz, 3 H), 1.28 (t, $J = 7.1$ Hz, 3 H):
H), 0.86 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 6.5 Hz, 3 H);

$^{13}C$ NMR (100 MHz, CDCl$_3$) δ 149.5, 145.3, 130.4, 127.1, 125.0, 118.3, 79.9, 75.6, 69.6, 49.4, 44.6, 42.5, 24.4, 22.6, 22.3, 21.9, 14.7, 11.5.

**Compound 4.11:** General procedure A was applied, starting with 32.2 mg (0.088 mmol) of 4.8. The crude mixture was purified by pTLC (silica gel, 5:1 hexanes/EtOAc, two elutions) to provide 11 mg of product (47% yield).

**Physical state:** white solid;

$R_f$ = 0.62 (5:1 hexanes/EtOAc);

m.p. = 208–210 °C;

HRMS (m/z): calcd for C$_{14}$H$_{16}$O$_3$SH$^+$ [M+H]$^+$, 265.0893; found, 265.0882;

IR (film) $\nu_{\text{max}}$= 1670, 1455, 1389, 1201, 836, 799, 723;

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.72 (d, J = 8.0 Hz, 1 H), 7.44 (s, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 5.86 (s, 1 H), 5.62 (ddd, J = 8.7, 5.0, 1.4 Hz, 1 H), 5.40 (s, 1 H), 4.94 (s, 1 H), 4.87 (s, 1H), 2.72 (dd, J = 14.8, 8.7 Hz, 1 H), 2.66 (dd, J = 14.8, 5.0 Hz, 1 H), 2.45 (s, 3 H), 1.83 (s, 3 H);

$^{13}C$ NMR (151 MHz, CDCl$_3$) δ 143.9, 139.3, 137.9, 133.6, 131.8, 130.1, 126.1, 124.6, 115.3, 115.0, 82.3, 42.0, 22.6, 21.9.
**Compound 4.12**: 1. In a flame-dried 5 mL vial, a mixture of cyclopentyl-ethanol (200 mg, 1.75 mmol, 1 equiv), ortho-nitro-benzenesulfonyl chloride (580 mg, 2.625 mmol, 1.5 equiv), DMAP (21.4 mg, 0.175 mmol, 0.1 equiv) was dissolved in THF (2.1 mL). To this solution, NEt$_3$ (441.8 mg, 0.6 mL, 4.375 mmol, 2.5 equiv) was added and the resulting mixture was allowed to stir at room temperature under Ar overnight (TLC control). Upon completion, the reaction was washed with sat NH$_4$Cl (3 mL) and extracted with EtOAc (3 x 3 mL). The organic solution was further washed with brine (5 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (silica gel, 10:1 hexanes/EtOAc) to yield 284.3 mg of desired product (54% yield, unoptimized).

2. The previously synthesized ortho-nitro tosylate (150 mg, 0.5 mmol, 1 equiv) was transferred to a flame-dried vial and kept under Ar. To this, Pd/C (10 mol%) (80 mg, 0.075 mmol, 0.15 equiv) was added and the vial was placed under high vacuum before being filled with H$_2$ (process repeated 3X). Upon addition of cyclohexane (10 mL), the heterogeneous solution was stirred at room temperature overnight (H$_2$ balloon). The resulting mixture was filtered through a plug of celite (eluted with EtOAc) and after evaporation of the solvent, 4.12 was obtained in 96% yield (129.4 mg).

**Physical state**: colorless oil;

$R_f = 0.40$ (4:1 hexanes/EtOAc);

**HRMS ($m/z$)**: calcd for C$_{13}$H$_{19}$NO$_3$SH$^+$/[M+H]$^+$, 270.1158; found, 270.1156;
IR (film) $\nu_{\text{max}}$ = 3488, 3387, 2948, 1623, 1484, 1348, 1174, 1161, 928;

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.70 (dd, $J$ = 8.0, 1.5 Hz, 1 H), 7.35 (ddd, $J$ = 8.6, 7.3, 1.6 Hz, 1 H), 6.82 – 6.71 (m, 2 H), 4.96 (bs, 2 H), 4.02 (t, $J$ = 6.7 Hz, 2 H), 1.81 (heptet, $J$ = 7.2 Hz, 1 H), 1.72 – 1.62 (m, 4 H), 1.60 – 1.51 (m, 2 H), 1.51 – 1.41 (m, 2 H), 1.07 – 0.95 (m, 2 H);

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 146.3, 135.2, 130.5, 117.4, 117.2, 116.9, 70.3, 36.3, 34.9, 32.4, 25.0.

**Compound 2.62**: A flame dried 5 mL vial was kept under Ar and charged with 4.12 (7.9 mg, 0.029 mmol, 1 equiv) which was dissolved in degassed CH$_3$NO$_2$ (1 mL) and the solution was cooled at 0 ºC before the dropwise addition of *tert*-BuONO (4.54 mg, 3.5 µL, 0.044 mmol, 1.5 equiv). The resulting bright yellow solution was stirred at 0 ºC for 10 min, then TEMPO (4.7 mg, 0.029 mmol, 1 equiv) was added in one portion to give a pale brown mixture. The reaction was then allowed to proceed at room temperature for 3h (TLC control). Upon completion, the crude mixture was concentrated *in vacuo* and dissolved in a solution of CDCl$_3$ (0.5 mL) containing trimethoxybenzene (3.28 mg/mL; 0.058 mmol/mL) as an internal standard and analyzed by $^1$H NMR to obtain a product yield (44%).

**Physical state**: colorless oil;

$R_f$ = 0.53 (4:1 hexanes/EtOAc);

**HRMS (m/z)**: calcld for C$_{13}$H$_{16}$O$_3$SNa$^+$ [M+Na]$^+$, 275.0712; found, 275.0712;
**IR (film)** ν\textsubscript{max} = 2952, 2846, 1448, 1358, 1184, 1096, 962;

**H NMR (600 MHz, CDCl\textsubscript{3})** δ 7.94 – 7.88 (m, 2 H), 7.66 (t, J = 7.5 Hz, 1 H), 7.56 (t, J = 7.8 Hz, 2 H), 5.35 (s, 1 H), 4.15 (t, J = 6.9 Hz, 2 H), 2.43 (t, J = 6.5 Hz, 2 H), 2.28 – 2.21 (m, 2 H), 2.14 (t, J = 6.6 Hz, 2 H), 1.80 (quintet, J = 9.6 Hz, 2 H);

**C NMR (151 MHz, CDCl\textsubscript{3})** δ 138.6, 136.3, 133.8, 129.3, 128.0, 126.7, 69.2, 35.0, 32.6, 30.6, 23.3.

Method for determining the enantioselectivity of the desaturated product, using (±)-3.16 and (−)-3.16:

**Column**: Daicel Chiralcel® OD

**Dimensions**: 4.6 × 250 mm

**Eluent**: 10% isopropanol 90% hexanes

**Flow rate**: 0.5 mL/min
Figure 5.1. Chromatogram of (±)-3.16 on a chiral column, showing ≈ 0% ee.
Figure 5.2. Chromatogram of \((-\)-3.16 on a chiral column, showing 98% ee.
Figure 5.3 X-ray structures.
Appendix
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$\text{Br} \quad \begin{array}{c}
\text{N} = \text{N} \\
\text{N} \quad \text{O}
\end{array}$

$^1\text{H NMR (600 MHz, CDCl}_3\text{)}$
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^1$H NMR (151 MHz, CDCl$_3$)

\[
\text{Chemical Structure:} \quad \begin{array}{c}
\text{SO}_2\text{Cl} \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\end{array}
\]

\[
\text{13C NMR (151 MHz, CDCl$_3$)}
\]
$^1$H NMR (600 MHz, CDCl$_3$)
${}^{13}\text{C NMR (151 MHz, CDCl}_2\text{)}$
$^{1}H$ NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
\[ ^1\text{H NMR (400 MHz, CDCl}_3 \text{)} \]
$^{1}H$ NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{1}$H NMR (400 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
\(^{13}\text{C NMR (151 MHz, CDCl}_3\)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{1}H$ NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{1}$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}\text{C NMR (151 MHz, CDCl}_3\text{)}$
$^1$H NMR (600 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{1}H$ NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
\[ \text{Me} \quad \text{OTs} \quad \text{Ph} \]

\(^1\text{H NMR (600 MHz, CDCl}_2\text{)}\)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}\text{C NMR} (151 \text{ MHz, CDCl}_3)$
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$\text{OTs}$

$^1\text{H NMR (600 MHz, CDCl}_3)$
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}\text{C NMR (151 MHz, CDCl}_3\text{)}$
$\text{H NMR (600 MHz, CDCl}_3\text{)}$
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$\text{Me} \text{C} = \text{NHTs}$

$\text{CO}_2\text{Bu}$

$^{13}\text{C NMR (151 MHz, CDCl}_3)$
\[ \text{\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3})} \]
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, DMSO-$d_6$)
$^{13}$C NMR (151 MHz, DMSO-$d_6$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (500 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1H$ NMR (600 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
1H NMR (600 MHz, CDCl₃)
$^{13}$C NMR (151 MHz, CDCl₃)
$\text{OSO}_2\text{Ph}$

$^1\text{H NMR (600 MHz, CDCl}_3$)
$^{13}$C NMR (151 MHz, CDCl$_3$)
Curriculum Vitae
Ana-Florina Voica

Current position: Ph.D. Candidate, Organic Chemistry
The Scripps Research Institute
Department of Chemistry
10550 North Torrey Pines Road, BCC-162
La Jolla, California 92037
Telephone: (858) 784-7371
Facsimile: (858) 784-7375
Email: avoica@scripps.edu

Date/Place of birth: 15 March 1985/ Slatina, Olt, Romania

Citizenship: Romania

Education

2007 – present THE SCRIPPS RESEARCH INSTITUTE, La Jolla, California
Ph.D. Graduate Student in Chemistry
(expected graduation date: May 2012)
Thesis: Guided Desaturation of Unactivated Aliphatics
Advisor: Professor Phil Baran

2003 – 2007 SMITH COLLEGE, Northampton, Massachusetts
B.A. with Highest Honors in Chemistry
B.A. in Biochemistry
GPA (overall in chemistry) 3.93/4
GPA (overall) 3.79/4, Cum Laude (overall)
Senior Thesis: Synthesis of Cobalt-Complexed Substrates for the Diels-Alder Reaction
Advisor: Professor Kevin Shea

2005 – 2006 SORBONNE UNIVERSITY, Paris, France (Junior Year Abroad)

Honors and Awards

• The Norman & Margaret Lassey Scholarship, Scripps, 2007 – 2008
• C. Pauline Burt Prize, Smith College, 2007
• Sigma Xi, Smith College, 2007
• Phi Beta Kappa, Smith College, 2006
• Dean’s List, Smith College, 2003 – 2007
• First Group Scholars (top 3% of class), Smith College, 2003 – 2006
• The Coulter Foundation Scholarship to study at Smith College, 2003 – 2007
• 2nd Prize, National Chemistry Olympiad, Romania, 2003
• 1st Prize, National Chemistry Olympiad, Romania, 2002
• Selection in the enlarged team for the International Chemistry Olympiad, Romania, 2002

Undergraduate Research Internships

Jun – Aug 2006                UNIVERSITY OF CAMBRIDGE, Cambridge, UK  
Advisor: Professor Steven Ley

Sept 2005 – May 2006           ÉCOLE NORMALE SUPERIEURE DE CHIMIE, Paris, France  
Advisor: Professor Jean-Pierre Genet

Jun – Aug 2004, 2005           SMITH COLLEGE, Northampton, Massachussets  
Advisor: Professor Kevin Shea

Publications

1. Voica, A.- F.; Mendoza, A.; Gutekunst, W. R.; Otero, J. F.; Baran, P. S. Guided Desaturation of Unactivated Aliphatics, Nat. Chem. accepted for publication.

2. Baxendale, I. R.; Ley, S. V.; Smith, C. D.; Tamborini, L.; Voica, A.- F. A Bifurcated Pathway to Thiazoles and Imidazoles using a Modular Flow Microreactor, J. Comb. Chem., 2008, 10, 851 – 857.

3. Maimone, T. H.; Voica, A.- F.; Baran, P. S. A Concise Approach to Vinigrol, Angew. Chem. Int. Ed., 2008, 47, 3054 – 3056.

4. Martinez, R.; Voica, A.- F.; Genet, J.- P.; Darses, S. Base-Free Mizoroki-Heck Reaction Catalyzed by Rhodium Complexes, Org. Lett., 2007, 9, 3213 – 3216.

Language Skills

• English (fluent)
• French (fluent)
• Spanish (reading, listening)
• Romanian (native language)
