STUDIES ON RADICAL REACTIONS FOR THE SYNTHESES OF
PHARMACEUTICALLY RELEVANT ORGANIC MOTIFS

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, the dissertation entitled:

**STUDIES ON RADICAL REACTIONS FOR THE SYNTHESSES OF PHARMACEUTICALLY RELEVANT ORGANIC MOTIFS**

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the degree of Doctor of Philosophy
in Chemistry

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Abstract

Organic synthesis plays a significant role in the pharmaceutical industry, particularly in providing a large array of pharmaceutically active molecules for drug discovery. In spite of numerous methods developed, there are still many limitations in the existing synthetic methodologies for pharmaceutically important organic motifs. Two such motifs are organofluorine derivatives and nitrogen heterocycles. This thesis focuses on my research on the development of new and efficient methodologies for the syntheses of these two motifs.

Chapter 2 describes the development of a new radical fluorodecarboxylation method using xenon difluoride. This method can efficiently convert 2-aryl-2-fluoroacetic acids with different substituents to difluoromethyl aryl ethers in good to excellent yields (53-80%).

Chapter 3 details studies on the mechanism of fluorine transfer in radical fluorinations by N-F reagents, including Selectfluor and N-fluorobenzenesulfonimide (NFSI). Two strategies, carbocation rearrangement and carbocation trapping, were applied to identify the possible carbocation intermediates during the fluorinations of alkyl radicals. The results of our studies are consistent with a fluorine atom transfer pathway between alkyl radicals and either Selectfluor or NFSI. Mechanistic studies into silver-catalyzed radical fluorination method indicated the formation of carbocations, presumably via a single electron transfer pathway between alkyl radicals and the silver catalyst. The carbocation formation was supported by the detection of the products from carbocation rearrangement as well as carbocation trapping by nucleophiles.

Chapter 4 describes the development of a novel 6-endo-trig radical cyclization onto hydrazones for the regio-controlled and stereoselective syntheses of tetrahydrophthalazines. Two
synthetic protocols using this radical cyclization were developed, including one-pot or stepwise processes, to access substituted tetrahydrophthalazines. These protocols showed good efficiency and robustness, and were able to afford high yields (50-98%) of the desired products with excellent functional group tolerance. This radical cyclization is also the first method to achieve excellent \textit{trans}-diastereoselectivity in the syntheses of 1,4-disubstituted tetrahydrophthalazines.

Chapter 5 describes the applications of the 6-\textit{endo-trig} radical cyclization for the syntheses of other nitrogen-containing motifs, such as tetrahydroazaphthalazines, tetrahydropyrazidines, dihydrophthalazines, aromatic phthalazines, and pyrazolo phthalazine diones. Additionally, we have developed a Pt-catalyzed hydrogenation for the cleavage of N-N bonds of the tetrahydrophthalazines, as a new route to 1,4-diamines.
Lay Summary

Organic synthesis has provided numerous innovative technologies for the production of pharmaceutical molecules. This thesis describes the studies on radical reactions for the syntheses of organofluorine compounds and nitrogen heterocycles, which have renowned pharmaceutical significance. In particular, our studies focus on the development of new and efficient radical methodologies, as well as the investigation of the mechanisms of relevant radical transformations for the development of innovative synthetic technologies in the future.
Preface

This thesis is written by Wei Zhang based on the scientific projects in the Prof. Glenn M. Sammis’ laboratory at the University of British Columbia. Prof. Glenn M. Sammis provided the overall design of the research projects, helpful suggestions during the course of the graduate research, and thoroughly edited this thesis. Chapter 2 is based on research performed in the Prof. Glenn Sammis’ laboratory with my colleagues Paul Foth and Manu Jagdeo. Part of the work in the Chapter 2 has been published as one aspect of a whole project in: Chatalova-Sazepin, C.; Binayeva, M.; Epifanov, M.; Zhang, W.; Foth, P.; Amador, C.; Jagdeo, M.; Boswell, B. R.; Sammis, G. M. *Org. Lett.* 2016, 18, 4570–4573. In this project, C. Chatalova-Sazepin, M. Binayeva, M. Epifanov, C. Amador, and B. R. Boswell contributed to the exploration of the syntheses of trifluoromethyl ethers, which is not included in this theses. In the Chapter 2 of this thesis, substrate 164c was prepared by P. Foth. M. Jagdeo contributed to the syntheses of substrates 164a and 164e. To obtain the average yields of aryl difluoromethyl ethers, M. Jagdeo performed the repeats of xenon fluoride-mediated fluorodecarboxylations of 2-aryloxy-2-fluoroacetic acids 164b and 164e, and P. Foth performed the repeat of xenon fluoride-mediated fluorodecarboxylation of 164c. All the other experiments and data analyses were carried out by W. Zhang.

Chapter 3 is based on research that was in collaboration between the Prof. Glenn M. Sammis’ laboratory and Prof. Chaozhong Li’s laboratory at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. All the work described in Chapter 3 was performed in
the Prof. Glenn M. Sammis’ laboratory and has not been published. All the experiments and data analyses in this chapter were carried out by W. Zhang.

Chapter 4 and Chapter 5 are based on research performed in the Prof. Glenn M. Sammis’ laboratory in collaboration with my colleague Jia Yi Mo, and Weiying He from Prof. Pierre Kennepohl’s Laboratory. A large part of the results in these two chapters have been published in: Zhang, W.; Mo, J. Y.; He, W.; Kennepohl, P.; Sammis, G. M. Chem. – Eur. J. 2018, chem.201805249. Substrates 312 and 314 were synthesized by J.-Y. Mo. Radical cyclization of 312 was scaled up to afford the purified 313 by J.-Y. Mo, who also performed COSY and nOe NMR spectroscopic analysis to determine the diastereochemistry of 313. The DFT calculations on the cyclization pathways of 312 in Chapter 4 were performed by Weiying He in the Prof. Pierre Kennepohl’s laboratory. All the other experiments and data analyses in Chapter 4 and 5 were performed by W. Zhang.
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<tr>
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<td>Ångstrom</td>
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<tr>
<td>Ac</td>
<td>Acetyl</td>
<td>acetyl</td>
</tr>
<tr>
<td>Acr</td>
<td>Acridinium</td>
<td>acridinium</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
<td>2,2'-azobisisobutyronitrile</td>
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<tr>
<td>Alloc</td>
<td>Allyloxy carbonyl</td>
<td>allyloxy carbonyl</td>
</tr>
<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid</td>
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<tr>
<td>aq.</td>
<td>Aqueous</td>
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<tr>
<td>Ar</td>
<td>Aryl</td>
<td>aryl</td>
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<tr>
<td>B3LYP</td>
<td>Becke 3-Parameter (Exchange), Lee, Yang and Parr</td>
<td>Becke 3-Parameter (Exchange), Lee, Yang and Parr</td>
</tr>
<tr>
<td>BDE</td>
<td>Bond dissociation energy</td>
<td>bond dissociation energy</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
<td>benzyl</td>
</tr>
<tr>
<td>br.</td>
<td>Broad</td>
<td>broad</td>
</tr>
<tr>
<td>Boc</td>
<td>t-Butyloxy carbonyl</td>
<td>t-Butyloxy carbonyl</td>
</tr>
<tr>
<td>BPMED</td>
<td>N,N-bis(phenylmethylene)-1,2-ethanediamine</td>
<td>N,N-bis(phenylmethylene)-1,2-ethanediamine</td>
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<tr>
<td>BPO</td>
<td>Benzoyl peroxide</td>
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<td>1,4-Benzoquinone</td>
<td>1,4-Benzoquinone</td>
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<tr>
<td>brsm</td>
<td>Based on recovered starting material</td>
<td>based on recovered starting material</td>
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<td>bpy</td>
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<td>Bz</td>
<td>Benzoyl</td>
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°C  degree Celsius

calcd.  calculated

CAS  Chemical Abstracts Service

cat.  catalyst

CBz  carbenzyloxy

CFL  compact fluorescent lamp

cLogP  calculated partition coefficient

CNS  central nervous system

Cp*  pentamethylcyclopentadienyl

CSA  (1S)-(+)−10-camphorsulfonic acid

Δ  heat

DAST  diethylaminosulfur trifluoride

DBU  1,8-diazabicyclo[5.4.0]undec-7-ene

DCM  dichloromethane

DCE  1,2-dichloroethane

DDQ  2,3-dichloro-5,6-dicyanobenzoquinone

DEAD  diethyl azodicarboxylate

(DHQD)$_2$PHAL  hydroquinidine 1,4-phthalazinediyl diether

DIPEA  diisopropylethylamine

DMA  dimethylacetamide

DMAP  4-dimethylaminopyridine

xxviii
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<th>Abbreviation</th>
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<tr>
<td>DMC</td>
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<tr>
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<td>$N,N$-dimethylformamide</td>
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<tr>
<td>DMS</td>
<td>dimethylsulfide</td>
</tr>
<tr>
<td>DTBP</td>
<td>di-$t$-butylperoxide</td>
</tr>
<tr>
<td>dtbpby</td>
<td>4,4-bis($t$-butyl)-2,2’-bipyridine</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
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<tr>
<td>DCC</td>
<td>$N,N$-dicyclohexylcarbodiimide</td>
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<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
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<td>equiv</td>
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<td>ESI</td>
<td>electrospray ionization</td>
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<td>EI</td>
<td>electron impact</td>
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<td>EWG</td>
<td>electron withdrawing group</td>
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<td>E°</td>
<td>standard reduction potential</td>
</tr>
<tr>
<td>EDG</td>
<td>electron donating group</td>
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<td>EPR</td>
<td>electron paramagnetic resonance</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>e</td>
<td>elementary charge</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>“F•”</td>
<td>atomic fluorine source(s)/radical fluorinating agent(s)</td>
</tr>
<tr>
<td>FAT</td>
<td>fluorine atom transfer</td>
</tr>
<tr>
<td>F-PBG</td>
<td>2-fluoroporphobilinogen</td>
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</table>
g gram(s)
GBq gigabecquerel
h hour(s)
HAT hydrogen atom transfer
HFIP 1,1,1,3,3,3-hexafluoro-2-propanol
HOMO highest occupied molecular orbital
HRMS high resolution mass spectrometry
HAT hydrogen atom transfer
HMPA hexamethylphosphoramide
Hz Hertz
$h\nu$ light
$i-$ iso-
IR infrared
k rate constant
$J$ coupling constant
L liter
LAH lithium aluminum hydride
LDA lithium diisopropylamide
LED light-emitting diode
LG leaving group(s)
Log $D$ distribution coefficient
<table>
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<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>µ</td>
<td>micro</td>
</tr>
<tr>
<td>m</td>
<td>milli or multiplet</td>
</tr>
<tr>
<td>m-</td>
<td>meta-</td>
</tr>
<tr>
<td>M</td>
<td>molarity or molecular weight</td>
</tr>
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<td>min</td>
<td>minute(s)</td>
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<td>Me</td>
<td>methyl</td>
</tr>
<tr>
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<td>MMPP</td>
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<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
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<tr>
<td>MS</td>
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<tr>
<td>m/z</td>
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<tr>
<td>NHPI</td>
<td>N-hydroxyphthalimide</td>
</tr>
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<td>N-methyl-2-pyrrolidone</td>
</tr>
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<td>Definition</td>
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<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
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<td>nuclear Overhauser effect</td>
</tr>
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<td>Ns</td>
<td>nitrobenzenesulfonyl</td>
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<tr>
<td>Nu</td>
<td>nucleophile</td>
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<td>o-</td>
<td><em>ortho-</em></td>
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<td>ox</td>
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<td><em>para-</em></td>
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</tr>
<tr>
<td>PG</td>
<td>protecting group(s)</td>
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<td>Ph</td>
<td>phenyl</td>
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<td>PhthN</td>
<td>phthalimide</td>
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<td>PIFA</td>
<td>phenyliodine bis(trifluoroacetate)</td>
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<td>PMPs</td>
<td><em>p</em>-methoxyphenylsulfonyl</td>
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<tr>
<td>PPHF</td>
<td>pyridinium poly(hydrogen fluoride)</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
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<td>Ps</td>
<td>phenylsulfonyl</td>
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<tr>
<td>q</td>
<td>quartet</td>
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<td>Red.</td>
<td>reduction</td>
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<tr>
<td>rt</td>
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<tr>
<td>RCY</td>
<td>radiochemical yield</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SA</td>
<td>specific activity</td>
</tr>
<tr>
<td>SCE</td>
<td>saturated calomel electrode</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>SHE</td>
<td>standard hydrogen electrode</td>
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<tr>
<td>S_N2</td>
<td>bimolecular nucleophilic substitution</td>
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<td>S_NAr</td>
<td>nucleophilic aromatic substitution</td>
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<tr>
<td>SOMO</td>
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<td>σ</td>
<td>bonding orbital</td>
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<tr>
<td>σ*</td>
<td>antibonding orbital</td>
</tr>
<tr>
<td>t</td>
<td>triplet or time</td>
</tr>
<tr>
<td>t</td>
<td>tertiary</td>
</tr>
<tr>
<td>T</td>
<td>temperature</td>
</tr>
<tr>
<td>TAS</td>
<td>tris(dimethylamino)sulfonium</td>
</tr>
<tr>
<td>TASF</td>
<td>tris(dimethylamino)sulfonium difluorotrimethylsiliconate</td>
</tr>
<tr>
<td>TBAF</td>
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<td>TBAI</td>
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<td>Abbreviation</td>
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<td>TBHP</td>
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<td>TBS</td>
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<td>TEDA</td>
<td>triethylenediamine</td>
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<td>TEMPO</td>
<td>(2,2,6,6-tetramethylpiperidin-1-yl)oxy</td>
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<td>Tf</td>
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<td>trifluoromethyl triflate</td>
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<td>tetrahydrofuran</td>
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<td>TMEDA</td>
<td>$N,N,N',N'$-tetramethylethane-1,2-diamine</td>
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<td>tetramesitylporphyrin</td>
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<td>tosyl</td>
</tr>
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<tr>
<td>UV</td>
<td>ultraviolet</td>
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<td>watt(s)</td>
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Acknowledgements

I would like to express my sincere gratitude to my supervisor, Prof. Glenn M. Sammis, for his constant support and trust throughout my graduate study. I deeply appreciate his enormous dedication to scientific research and education. From him, I learnt what it is to be a scientist, especially the perseverance, passion, and critical thinking. His endless enthusiasm and support have motivated me both professionally and personally to aim high and achieve more. It has been a great pleasure and privilege to have him as my mentor.

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To my beloved parents

whose immense diligence and kindness influence me to become who I am.

致我敬爱的父母

感谢他们的辛勤和关爱！
Chapter 1: Introduction

“La chimie crée son objet. Cette faculté créatrice, semblable à celle de l'art lui-même, la distingue essentiellement des sciences naturelles et historiques”

—Marcelin Berthelot (1860)

“In the century that has passed since Berthelot’s words were uttered, organic chemistry has literally placed a new Nature beside the old. And not only for the delectation and information of its devotees; the whole face and manner of society has been altered by its products……

We shall leave it that the evidence is overwhelming that the creative function of organic chemistry will continue to augment Nature, with great rewards, for mankind and the chemist in equal measure.”

—Robert Burns Woodward (1956)

Pharmaceuticals are an indispensable and significant part of the modern society. In contrast to ancient medicines that were usually extracted from plants or animals, modern pharmaceuticals have been largely produced through chemical synthesis, a scientific practise to construct molecules through chemical reactions. The earliest synthetic pharmaceuticals were antipyrine and aspirin, which date back to the end of 19th century. Over the past century, pharmaceutical development has been revolutionized by synthetic chemistry, which now allows rational design and syntheses of molecules, and enables rapid access to more expansive realm of chemical matters for the discovery of innovative pharmaceuticals. The significance of synthetic chemistry has been evidenced by the recognition of Nobel Prize in chemistry in 1965, 1990, 2001, 2005 and 2010, for the innovations on total synthesis and pharmaceutically relevant synthetic methodologies.
In spite of those breakthroughs, pharmaceutical development still faces significant challenges. Particularly, the limitations and insufficiency of available synthetic methodologies often impede the exploration of diverse molecular complexity and new chemical space in drug discovery process.\textsuperscript{3,6}

Organic synthesis has primarily focused on two electron processes (ionic),\textsuperscript{4,5} while single electron (radical) processes have been long sidelined in scientific research in the 20\textsuperscript{th} century.\textsuperscript{8,9} The lack of development of single electron processes is mainly attributed to the perception that radical species are chaotic and uncontrollable in chemical reactions. However, an increasing number of studies have demonstrated that radical reactions generally possess orthogonal reactivity profiles compared to ionic reactions, and demonstrate appealing synthetic versatility.\textsuperscript{8,10,11} This has led to the development of many novel radical synthetic methodologies.\textsuperscript{12}

The Sammis laboratory has focused on radical methodologies, especially the methods that are applicable to the syntheses of pharmaceutically important structures, such as organofluorine motifs\textsuperscript{13-16} and heterocycles.\textsuperscript{17,18} This thesis will present my studies on radical reactions for the syntheses of pharmaceutically relevant organic motifs, including alkyl fluorides, trifluoromethyl ethers, and phthalazine derivatives. The following sections will provide an overview on the aspects of both radical and fluorine chemistry that are relevant to my thesis, and how these fields interplay in the development of innovative synthetic methodologies.

1.1 General aspects of free radicals

Free radicals are a special type of reactive chemical species that possess unpaired single electrons in an atomic or molecular orbital (Figure 1.1). Free radicals can be generated in a number
of different ways, including through *homolytic bond cleavage* (*homolysis*), or from the corresponding cations or anions through redox processes via *single electron transfer* (SET) (Figure 1.1).\(^{19}\)

![Figure 1.1. Formation of free radical by homolysis and SET, and orbital illustration of carbocation, carbon radical and carbanion.](image)

The existence of free radicals was first hypothesized in the nineteenth century,\(^ {20,21}\) but the experimental evidence was not found to support it until 1849 when Kolbe conducted electrolytic decarboxylation of potassium acetate to form ethane.\(^ {22}\) However, skepticism still lingered for about half a century till a breakthrough came in 1900 when the triphenylmethyl radical (2) was synthesized and shown to exist in equilibrium with its dimer 3 in solution (Scheme 1.1).\(^ {23}\)

![Scheme 1.1. Formation of triphenyl methyl radical and its dimer by Gomberg.](image)
Another significant report was published in 1929 by Paneth, who conducted the decomposition of tetramethyllead (4) in an inert gas at 450 °C (Scheme 1.2).\textsuperscript{24} It was observed that elemental lead was generated at a high temperature, but could be converted back to tetramethyllead at a lower temperature. This experiment supported the existence of methyl radicals in the gas phase. After this early experimental evidence, free radicals had been gradually accepted as general chemical species and integrated into the study of theoretical and practical chemistry problems.

\begin{equation*}
\begin{array}{ccc}
\text{Pb(CH}_3\text{)}_4\text{(g)} & \xrightarrow{450 \degree C} & \text{Pb}_{(s)} + 4 \text{ Me•}_{(g)} \\
4 \text{ Me•}_{(g)} + \text{Pb}_{(s)} & \xrightarrow{100 \degree C} & \frac{\text{Pb(CH}_3\text{)}_4\text{(g)}}{4}
\end{array}
\end{equation*}

\textbf{Scheme 1.2.} Decomposition and re-formation of tetramethyllead by Paneth.

Free radicals are usually present as reactive intermediates in chemical reactions. Similar to other reactive chemical intermediates, free radicals are often short-lived, highly energetic and chemically reactive, since they do not fulfill the octet rule.\textsuperscript{25} Free radicals can be converted to different reactive intermediates, including new radical species through reactions such as radical substitution, addition, fragmentation, or carbocations and carbanions through redox processes. It will usually lead to neutral molecules through termination reaction, such as radical dimerization and disproportion.

Of all the radical reactions, chain reactions are the most common type. Chain reactions consist of three phases: initiation, propagation and termination (Scheme 1.3).\textsuperscript{26} The initiation phase involves the reaction of an initiator to form free radicals, $X \cdot$ and $Y \cdot$ via \textit{homolysis} of a covalent bond. In the propagation phase, $X \cdot$ participates in any number of radical transformations, and also
regenerates $X\cdot$ in order to continue the chain process. The termination phase ends a chain reaction by forming an inactive species, through processes such as dimerization or disproportionation.

\[
\begin{align*}
\text{Initiation} & \quad X-Y \quad \rightarrow \quad X\cdot + Y\cdot \\
\text{Propagation} & \quad \begin{cases} 
X\cdot + A-R & \quad \rightarrow \quad X-A + R\cdot \\
R\cdot + X-Y & \quad \rightarrow \quad R-Y + X\cdot 
\end{cases} \\
\text{Termination} & \quad \begin{cases} 
2X\cdot & \quad \rightarrow \quad X-X \\
2R\cdot & \quad \rightarrow \quad R-R \\
R\cdot + X\cdot & \quad \rightarrow \quad R-X
\end{cases}
\end{align*}
\]

**Scheme 1.3.** Mechanistic illustration of radical chain reactions.

### 1.1.1 Types of free radicals

There are three kinds of radicals that are typically involved in organic reactions, i.e. neutral, cationic and anionic radicals (Figure 1.2).

**Figure 1.2.** Representative examples of neutral radical, cation radical and anion radical.

Free radicals can be further divided into $\sigma$ radicals and $\pi$ radicals, based on the molecular orbitals where the unpaired electrons reside; $\sigma$ radicals have unpaired electrons in the $\sigma$ orbitals and $\pi$ radicals have unpaired electrons in the $\pi$ orbitals. For example, phenyl radical is a typical $\sigma$ radical and benzyl radical is a $\pi$ radical since the unpaired single electron is in a $\rho$ orbital and is conjugated with the $\pi$ orbitals of the phenyl ring (Figure 1.3).
Most of the radicals described thus far are *transient radicals*, or radicals that are reactive and have short life-times. Another class of radicals, *persistent radicals*, have long life-times as they are resistant to dimerization, disproportionation, or other self-annihilation processes. The long life-times of persistent radicals are usually due to multiple effects, such as steric hindrance, conjugation/hyperconjugation or poor reactivity. For instance, triphenyl methyl radical can be indefinitely persistent in the absence of molecular oxygen, due to the bulky substitution environment of the radical center and poor reactivity to form C-Y bonds.

### 1.1.2 Characteristics of free radicals

*Stereochemistry*

The geometry of free radicals has been extensively studied by *Electron Spin Resonance* (ESR) spectroscopy and other spectroscopic methods. Normally alkyl radicals without resonance stabilization are in pyramidal shapes (Figure 1.4), with the exception of methyl radical that has a planar structure according to microwave studies and MO calculations. As the size of the substituents on the radical centers increase, the shapes of alkyl radicals become successively more pyramidal due to the increasing steric repulsion. Generally, pyramidal alkyl radicals without structural constraints can rapidly undergo inversion. For instance, the calculated inversion barriers of tert-butyl and trichloromethyl radicals are only 1.8 and 2.3 kcal/mol, respectively.
The geometry of free radicals can be significantly influenced by the types of substituents α to the radical. Heteroatom substituents, such as fluorine and oxygen, lead to pyramidal shapes at the radical center.\textsuperscript{33,34} According to ESR spectroscopic studies, increasing the number of fluorine substituents on a methyl radical results in progressive distortion from the original planar shape. The geometric effects of heteroatoms are mainly attributed to the electronic repulsion between the singly-occupied $p$ orbitals on radical centers and the lone electron pairs of heteroatoms, which can be alleviated through the adoption of pyramidal structures and increasing the degree of $sp^3$ hybridization of the singly-occupied $p$ orbitals. Pyramidal shapes could be further enhanced by the stabilizing interaction between singly-occupied $p$ orbitals and $\sigma^*$ antibonding orbitals of the C–X bonds. α-Substituents that can conjugate with the radical center, such as aromatic rings, alkenes and carbonyl-type groups, lead to trigonal planar alkyl radicals (see Ph–CH$_2$• in Figure 1.3).\textsuperscript{35}

Alkenyl and aryl radicals are both $sp^2$ carbon-centered radicals. Aryl radicals have the singly-occupied molecular orbitals in the plane of the aromatic ring (see Ph• in Figure 1.3). Alkenyl radicals also have planar structures, but the C=C–H angles are generally enlarged (137° for vinyl radical),\textsuperscript{36} compared to the geometry of corresponding alkenes. Alkenyl radicals are flexible enough to undergo cis/trans inversion with low energy barriers (0–2 kcal) (Scheme 1.4).\textsuperscript{37} This feature of alkenyl radicals has been applied to the development of geometrically convergent radical
reactions using mixed geometric isomers of alkene substrates.\textsuperscript{38} Alkynyl radicals are linear, and the unpaired electron lies in an $sp$ hybridized $\sigma$ orbital.

\[ \text{via:} \left[ \begin{array}{c} R^1 \\ R^2 \\ R^3 \end{array} \right]^* \]

\[ \Delta \Delta G^\ddagger = 0\text{--}2 \text{ kcal/mol} \]

\begin{center}
\textbf{Scheme 1.4.} Geometric inversion of alkenyl radical.
\end{center}

\textit{Stability/Reactivity}

The stability and reactivity of free radicals can be generally indicated by the strength of the corresponding covalent hydrogen bonds, namely the bond dissociation energy (BDE). The stability of free radicals varies significantly and is largely dependent on the nature of the atoms at the radical centers and the substitutions, as shown by the large range of BDEs of different covalent bonds (Table 1.1).\textsuperscript{39} The stability of free radicals are significantly affected by the hybridization of the radical centers, as can be seen by comparison of the BDEs of alkynyl, vinyl/aryl and alkyl C-H bonds (Table 1.1, Type 1). The stability of alkyl radicals increases with increasing substitution, which is shown by the BDEs of the C-H bonds, methyl $<$ primary $<$ secondary $<$ tertiary (Table 1.1, Type 1). Heteroatom substituents on the radical centers can stabilize the radicals because of the resonance effect of the lone electron pairs (Table 1.1, Type 1). Unsaturated groups, such as phenyl, vinyl, carbonyl, cyano, on the carbon centers can significantly decrease the BDEs, and render good stability for the corresponding radicals (Table 1.1, Type 1).
Table 1.1. Representative data of Bond dissociation energy (BDE) of covalent bonds.39

<table>
<thead>
<tr>
<th>BDEs (kcal/mol)</th>
<th>BDEs (kcal/mol)</th>
<th>BDEs (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1: C-H bonds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃—H</td>
<td>105</td>
<td>Allyl—H</td>
</tr>
<tr>
<td>Et—H</td>
<td>101</td>
<td>Bn—H</td>
</tr>
<tr>
<td>i-Pr—H</td>
<td>98</td>
<td>Ph₃C—H</td>
</tr>
<tr>
<td>t-Bu—H</td>
<td>96</td>
<td>Cyclohexa-1,4-dienyl—H</td>
</tr>
<tr>
<td>CFH₂—H</td>
<td>101</td>
<td>CH=CH₂—H</td>
</tr>
<tr>
<td>CF₃—H</td>
<td>103</td>
<td>CH₃OCH₂—H</td>
</tr>
<tr>
<td>CF₃—H</td>
<td>106</td>
<td>CF₃OCH₂—H</td>
</tr>
<tr>
<td>CCl₃—H</td>
<td>94</td>
<td>CF₃OCF₂—H</td>
</tr>
<tr>
<td>H₂N—H</td>
<td>108</td>
<td>F—H</td>
</tr>
<tr>
<td>H₂NNH—H</td>
<td>81</td>
<td>Cl—H</td>
</tr>
<tr>
<td>HO—H</td>
<td>119</td>
<td>Br—H</td>
</tr>
<tr>
<td>HO₂—H</td>
<td>88</td>
<td>I—H</td>
</tr>
<tr>
<td>CH₃O—H</td>
<td>105</td>
<td>TEMPO—H</td>
</tr>
<tr>
<td>PhO—H</td>
<td>87</td>
<td>CH₃COO—H</td>
</tr>
<tr>
<td><strong>Type 3: C-X bonds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃—CH₃</td>
<td>90</td>
<td>Ph—Ph</td>
</tr>
<tr>
<td>CH₃—NH₂</td>
<td>85</td>
<td>Ph—F</td>
</tr>
<tr>
<td>CH₃—OH</td>
<td>92</td>
<td>Ph—Cl</td>
</tr>
<tr>
<td>CH₃—F</td>
<td>110</td>
<td>Ph—Br</td>
</tr>
<tr>
<td>CH₃—SH</td>
<td>75</td>
<td>Ph—I</td>
</tr>
<tr>
<td>PhCH₂—F</td>
<td>99</td>
<td>C₆F₅—F</td>
</tr>
<tr>
<td>CF₃—F</td>
<td>131</td>
<td>CCl₃—Cl</td>
</tr>
<tr>
<td><strong>Type 4: X-X/X-Y bonds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F—F</td>
<td>38</td>
<td>t-BuO—OH</td>
</tr>
<tr>
<td>Cl—Cl</td>
<td>58</td>
<td>C₁₀H₂₁CO₂—O₂CC₁₀H₂₁</td>
</tr>
<tr>
<td>Br—Br</td>
<td>46</td>
<td>BzO—OBz</td>
</tr>
<tr>
<td>I—I</td>
<td>36</td>
<td>CH₃CO₂—OH</td>
</tr>
<tr>
<td>HO—OH</td>
<td>47</td>
<td>C₃H₃*N—O</td>
</tr>
<tr>
<td>H₂N—NH₂</td>
<td>66</td>
<td>CH₃O—NO</td>
</tr>
<tr>
<td>HS—SH</td>
<td>65</td>
<td>CH₃O—NH₂</td>
</tr>
<tr>
<td>t-BuO—O-t-Bu</td>
<td>39</td>
<td>CF₃O—F</td>
</tr>
<tr>
<td>‘O₃SO—OSO₃’</td>
<td>29</td>
<td>CH₃O—Cl</td>
</tr>
</tbody>
</table>

The nature of atoms at the radical centers is crucial for their stability. The BDEs of covalent bonds increase significantly in the order of N-H, O-H and F-H (Table 1.1, Type 2). The same
trend can be found in the halogen atoms from F to I (Table 1.1, Type 2), with F-H being the strongest bond and F• being the most unstable of the halide radicals. The BDEs of the commonly used metal hydrides, such as (TMS)₃Si-H, n-Bu₃Sn-H, (CH₃)₃Ge-H, are smaller than common covalent X-H bonds (Table 1.1, Type 2), making these hydride reagents excellent atomic hydrogen sources.

### 1.1.3 Generation of free radicals

**Peroxides and aza compounds**

As was mentioned in section 1.1, the homolysis of covalent bonds is one of the main ways to generate free radicals. The two most commonly utilized free radical precursors are azo compounds and peroxides (Table 1.2). Azo compounds, under thermal or photochemical conditions, can undergo homolysis to produce molecular nitrogen and two free radicals (Scheme 1.5). Azobisisobutyronitrile (AIBN) is an azo compound often used as an initiator in radical reactions. The stabilizing effect of cyano group on the resultant radicals and the formation of nitrogen gas, contribute to the facile homolysis of C-N bonds of AIBN.

\[
\begin{align*}
R^1\text{N} & \text{N} \quad R^2 & \xrightarrow{\Delta \text{ or } hv} & R^1\cdot & + & N_2 & + & R^2\cdot \\
\text{NC} & \text{N} & \text{CN} & \xrightarrow{\Delta} & 2 \text{NC}\cdot & + & N_2
\end{align*}
\]

**Scheme 1.5.** Homolysis of diazo compound, exemplified by AIBN.
Table 1.2. Representative examples of peroxides and azo compounds with decomposition rate and 10-hour half-life temperatures.\textsuperscript{40}

<table>
<thead>
<tr>
<th>Compound</th>
<th>(k_d(\text{s}^{-1}))</th>
<th>(T\ (\degree C))</th>
<th>Solvent</th>
<th>(T) of 10 h half-life (\degree C), solvent</th>
</tr>
</thead>
</table>
| \begin{array}{c}
\text{NC} \quad \text{N} \quad \text{N} \\
\text{CN} \quad \text{N} \quad \text{N} \\
\text{CN}
\end{array} & 3.2 \times 10^{-5} & 70 & \text{toluene} & 65, \text{toluene} \\
| \begin{array}{c}
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{O} \\
\text{Ph} \quad \text{O} \quad \text{O} \quad \text{O}
\end{array} & 2.3 \times 10^{-5} & 78 & \text{benzene} & 70, \text{benzene} \\
| \begin{array}{c}
\text{O} \quad \text{O} \quad \text{H}
\end{array} & 3 \times 10^{-7} & 130 & \text{benzene} & 170, \text{benzene} \\
| \begin{array}{c}
\text{O} \quad \text{O} \quad \\
\text{O}
\end{array} & 7.8 \times 10^{-8} & 80 & \text{benzene} & 125, \text{benzene} \\
| \begin{array}{c}
\text{O} \quad \text{O} \quad \\
\text{O}
\end{array} & 1.2 \times 10^{-6} & 85 & \text{benzene} & 100, \text{benzene} \\
| \begin{array}{c}
\text{O} \quad \text{O} \quad \text{O} \\
\text{O} \quad \text{O} \quad \text{O}
\end{array} & 3.8 \times 10^{-4} & 85 & \text{benzene} & 65, \text{benzene} \\
| \begin{array}{c}
\text{K}^+ \quad \text{O} \quad \text{O} \\
\text{O} \quad \text{O} \quad \text{K}^+
\end{array} & 6.9 \times 10^{-5} & 80 & \text{water} & 60, \text{water} \\
Peroxides, such as hydrogen peroxide, tert-butyl hydroperoxide, di-tert-butyl peroxide, benzoyl peroxide (7), and lauroyl peroxide, are also commonly utilized sources of free radicals. The O-O bonds in these peroxides are weak (BDE ~ 30 kcal/mol) and can be cleaved homolytically under photochemical conditions or at relatively low temperatures (60 – 150 °C) with half-lifes short enough for practical applications in organic reactions (Table 1.2). For instance, benzoyl peroxide (7) can be converted to two oxygen-centered benzoyl radicals (8) under thermal conditions, and further generate two carbon-centered phenyl radicals after the release of carbon dioxide (Scheme 1.6). This is a process often used in the initiation phase of radical chain reactions, especially for radical polymerization.42

\[ \text{Scheme 1.6. Thermal or photo homolysis of benzoyl peroxide to generate radical species.} \]

Peroxides can also participate in redox reactions to generate alkoxyl radicals effectively. For instance, it has been reported that tert-butyl hydroperoxide and hydrogen peroxide can react with redox-active transition metal salts, such as FeCl₃, to form tert-butoxy or hydroxyl radicals, together with hydroxide as a result of reduction by the transition metal salts (Scheme 1.7).43

\[ \text{Scheme 1.7. Reaction of hydroperoxide with transition metal salt to form oxygen-centered radical.} \]

Trialkylboranes

Trialkylboranes, such as triethylborane and 9-borabicyclo[3.3.1]nonane (9-BBN) have also been demonstrated to be good precursors of free radicals via oxidative processes.44 The generally accepted mechanism of radical formation involves the reaction between molecular oxygen (triplet
diradical) with trialkyl borane to generate one alkyl radical and a boron peroxy radical (Scheme 1.8). Compared to the radical formation from peroxides or azo compounds, the trialkylborane/oxygen system can form radicals at much lower temperatures, such as room temperature or \(-78^\circ\text{C}\).

\[
R_3B + O_2 \rightarrow R_3B-O-O\cdot + R\cdot
\]

**Scheme 1.8.** Trialkylborane reacts with oxygen gas to form alkyl radical and peroxy radical.

**Transition metal systems**

Transition metals have shown good versatility in the formation of organic radicals via redox processes. The initial discovery of triphenyl methyl radical resulted from a SET process between triphenyl methyl chloride and silver metal (Scheme 1.2). Other transition metal systems, such as iron and copper, have also been found redox active toward different types of organic molecules. For instance, Minisci studied the iron-catalyzed Kharasch reaction in atom-transfer alkene radical addition (Scheme 1.9). The reaction was initiated by chlorine atom transfer between tetrachloromethane (9) and Fe(II)Cl\(_2\) to form a trichloromethyl radical (12) and Fe(III)Cl\(_3\). Then, trichloromethyl radical undergoes radical addition to an alkene to generate a new alkyl radical 13. A subsequent chlorine atom abstraction from Fe(III)Cl\(_3\) affords the chlorotrichloromethylated product 11 and Fe(II)Cl\(_2\). Many other systems of transition metals, such as Cu, Mn, Ti, Ag, Ru, Ni, Co, are also able to catalyze or promote Kharasch-type reactions, and other radical reactions via redox processes. Photoactive organic and transition metal-based dyes have been shown to be effective for redox reactions with organic molecules under light irradiation, providing new methods for radical formation.
Samarium diiodide

Samarium(II) diiodide (SmI₂), discovered by Kagan,⁵⁰,⁵¹ has proved to be a powerful reducing reagent to generate carbon-centered radicals from either organohalides or carbonyl compounds (Scheme 1.10).⁵²,⁵³ SmI₂ has a high affinity toward oxygen atoms, which makes it often able to achieve a high degree of chemo- and stereoselectivity. Moreover, the reactivity of SmI₂ can be finely tuned and modulated for different synthetic purposes, by additives such as metal salts and protic molecules.⁵²-⁵⁵

**Scheme 1.10.** Samarium diiodide-mediated radical addition and ketone reduction.
1.1.4  Fundamental transformations of free radicals

Free radicals can participate in a myriad of chemical reactions, but the basic radical transformations can be categorized as radical substitution/atom abstraction, radical addition, or radical fragmentation. Each of these transformations will be summarized in the following sections.

Radical substitution/Atom abstraction

Radical substitution is a reaction of one free radical abstracting an atom from a non-radical species to form a new radical and another non-radical species (Scheme 1.11). This process involves the interaction of the singly-occupied molecular orbital (SOMO) of radical R• with the antibonding orbital of a covalent bond, X-Y, which triggers the homolytic cleavage of X-Y (Scheme 1.11).

\[
R^• + X-Y \rightarrow R-X + Y^•
\]

Scheme 1.11. Illustration of radical substitution and orbital interaction of the transition state.

Atom abstraction can happen in intramolecular reactions as well and 1,5-hydrogen atom transfer (1,5-HAT, Scheme 1.12) is the most common case due to the favorable six-membered transition state of this process, while 1,4 or 1,6-HAT have also been in radical reactions.\(^{56}\)

\[
\begin{array}{c}
\begin{array}{c}
\text{R}^\bullet \text{H} \\
\text{X} \\
\end{array}
\end{array}
\rightarrow
\begin{array}{c}
\begin{array}{c}
\text{R} \\
\text{H} \\
\end{array}
\end{array}
\]

\(X = O, NR\)

Scheme 1.12. Illustration of 1,5-HAT.
Radical addition

Radical addition is a reaction in which a free radical adds into an unsaturated system to form a new radical, as is the case of the intermolecular addition shown in Scheme 1.9 or the radical cyclization shown in Scheme 1.13. Generally, radical cyclizations are kinetically controlled processes. For instance, the 5-exo-trig radical cyclization is more favored than the competing 6-endo-trig cyclization, though the latter affords more stable secondary radical species. Radical addition and cyclization to aromatic rings are much slower than to alkenes, as the aromatic stabilization energies of the rings render it difficult for radical addition.

\[
\begin{align*}
\cdot & \quad \rightarrow \\
\text{98\%} & \quad \text{2\%}
\end{align*}
\]

**Scheme 1.13.** Radical cyclization in favor of 5-exo-trig than 6-endo-trig.

Radical fragmentation/rearrangement

Radical fragmentation involves a $\beta$-scission of a radical to afford a new radical and an unsaturated bond, which are usually more stable (Scheme 1.14). For instance, Hunsdiecker reaction involves the formation of carboxyl radical before $\beta$-scission to form a carbon-centered radical with the release of carbon dioxide gas (Scheme 1.14, 1). Also, a tert-butoxy radical can be converted to a methyl radical and an acetone molecule via $\beta$-scission (Scheme 1.14, 2).

\[
\begin{align*}
\text{(1)} & \quad \rightarrow \\
\text{(2)} & \quad \rightarrow
\end{align*}
\]

**Scheme 1.14.** Examples of radical fragmentation via $\beta$-scission.
Radical rearrangement reactions are less common compared to carbocation rearrangements. However, free radicals with certain structural features can undergo rearrangement via ring-opening and functional group migration. For instance, a cyclopropyl methyl radical can undergo rapid ring-opening reaction via $\beta$-scission ($k = 9.4 \times 10^7 \text{s}^{-1}$ at 25 °C), due to the ring strain, which makes it often used as a radical clock to indicate or prove the formation of radical intermediates (Scheme 1.15, 1). Radicals with unsaturated substituents, such as phenyl or vinyl, can undergo 1,n-migration via cyclic intermediates formed through exo radical cyclization. For example, 1,2-migration of phenyl and vinyl group can occur through cyclopropyl intermediates (Scheme 1.15, 2 and 3), but with much different rate constants (aryl: $k = 760 \text{s}^{-1}$ at 25 °C; vinyl: $k = 10^7 \text{s}^{-1}$ at 25 °C). Carbonyls can undergo 1,2-migration very fast through cyclopropoxy radical intermediates, but radical 1,2-migration with alkynyl and cyano groups are much slower.

Scheme 1.15. Examples of radical rearrangement.

1.1.5 Radical chemistry in modern organic synthesis

Ever since the initial discoveries of free radicals by Gomberg and Paneth at the beginning of 20th century, radical chemistry has attracted increasing interest in scientific research, and has been experiencing rapid development, especially in organic synthesis in the last four decades. The development has been demonstrated not only in the improved understanding of properties and
mechanisms of radical reactions, but also in many discoveries of new synthetic methods and their applications in the syntheses of complex molecules. For instance, in the 1980s, Curran et al. made remarkable achievements in the total syntheses of natural products by the ingenious designs and applications of radical cyclizations, and excellently demonstrated the power of organotin hydride-mediated radical chain reactions in the formation of multiple C–C bonds (the total synthesis of hirsutene (22) as an example, see Scheme 1.16).

Scheme 1.16. Total synthesis of (±)-hirsutene (22) using tandem radical cyclization by Curran et al.

Transition metal redox systems have also demonstrated great versatility for radical reactions, and have contributed to numerous innovations of radical synthetic methodologies. In particular, in the last decade visible light-mediated photoredox catalysis has been a key technology for the new generation of radical methods that use visible light and mild conditions for organic synthesis that are challenging for traditional radical reaction systems. Additionally, the renaissance of transition metal-catalyzed radical cross-coupling reactions have demonstrated the capability of integrating radical processes with less-expensive transition metal catalysis for the invention of diverse new and efficient synthetic technologies.
1.2 General aspects of fluorine chemistry

Fluorine has the second smallest atomic size (after hydrogen) and the largest electronegativity in the periodic table (Figure 1.5), and has developed into an important and active subject in both the frontier scientific research and chemical industry. In particular, organofluorine molecules have attracted considerable attention and have been successfully utilized in industrial applications. Fluorine-containing polymers and small molecules have been ubiquitously utilized in material applications, such as thermoplastics, coatings, refrigerants, and extinguishants. In addition, fluorine has become a prevalent and important component in drugs and agrochemicals due to its substantial impact on the physicochemical and biological properties of organic molecules. More than 20% pharmaceuticals and 30% agrochemicals on the market today contain fluorine. Additionally, the $^{18}$F isotope has been widely used in positron emission tomography (PET), a non-invasive molecular imaging technique.

![Fluorine atom and its properties.](image)

The industrial importance of fluorine has driven the development of various methods and fluorinating agents for the syntheses of organofluorine compounds. These methods range from traditional nucleophilic substitution to transition metal catalysis and radical reactions for controlled and selective fluorination. Fluorinating agents have also evolved from fluoride salts and elemental fluorine to many different kinds of safe, easy-to-handle and commercially available reagents. Overall, fluorine chemistry has been experiencing prosperous advancement and innovation in the contribution to the modern organic synthesis.
1.2.1 Brief history of fluorine chemistry

Fluorine is the 13\textsuperscript{th} most abundant element in the Earth’s crust and is found exclusively as a fluoride ion (F\textsuperscript{–}) in minerals. These mineral fluorides were discovered and used as early as 1529 when fluorite was an additive used to help lower the melting points of metals in smelting processes, from which it was penned the Latin name ‘fluorés’, meaning ‘flow’. Calcium difluoride was later determined to be the main composition of fluorite.\textsuperscript{76} By the 17\textsuperscript{th} century, it was known that glass would be etched when exposed to an acid generated from fluorite and sulfuric acid. However, it was not until 1810 that Ampère recognized that the resultant acid contained a new element analogous to chlorine, later named as ‘fluorine’.\textsuperscript{76,77} Isolation of molecular fluorine had been extremely difficult, due to the danger of both elemental fluorine and hydrogen fluoride, and the lack of proper fluoride electrolytes for electrolysis. After more than 70 years of effort by many chemists, elemental fluorine was successfully isolated by Moissan in 1886 via electrolysis of a melt mixture of potassium hydrogen difluoride and hydrogen fluoride (Figure 1.6),\textsuperscript{78,79} a feat that earned him the Nobel Prize in 1906.\textsuperscript{80} The isolation of elemental fluorine marked the beginning of modern fluorine chemistry. In the ensuing years, numerous significant advancements were made using molecular fluorine, including the important applications in Simmon’s fluorocarbon synthesis,\textsuperscript{81,82} and various applications in the syntheses of organofluorine molecules.\textsuperscript{83–86} The first purely chemical synthesis of elemental fluorine was achieved in 1986, when Christe applied a displacement reaction between K\textsubscript{3}MnF\textsubscript{6} and SbF\textsubscript{5} for the generation of F\textsubscript{2} in excess of 40\% yield.\textsuperscript{87}
In 1835, Dumas and Péligot accomplished the first synthesis of an organofluorine compound, methyl fluoride, from dimethyl sulfate and potassium fluoride (Scheme 1.17, 1). Later in 1862, Borodin, a well-known music composer, carried out the first halogen exchange experiment for the synthesis of benzoyl fluoride from benzoyl chloride in the presence of potassium hydrogen difluoride (Scheme 1.17, 2). In 1870, the first synthesis of aryl fluoride was achieved by Schmitt and von Gehren, via thermolysis of aryl diazonium salt with hydrofluoric acid, and this result was repeated and confirmed by Lenz in 1877 (Scheme 1.17, 3). This reaction suffered from low yields due to the poor nucleophilicity of solvated fluoride ion and competing reaction from water. This problem was later addressed by Balz and Schiemann in 1927 by using a fluoroboric acid or its salts, instead of hydrofluoric acid, to synthesize aryl fluorides.

\[
\text{HF} + \text{KHF}_2 \xrightarrow{\text{electrolysis}} \text{F}_2 \uparrow + \text{H}_2 \uparrow + \text{KF}
\]

Figure 1.6. Isolation of elemental fluorine via electrolysis by Moissan in 1886.    

1.2.2 Organofluorine chemistry

In 1835, Dumas and Peligot accomplished the first synthesis of an organofluorine compound, methyl fluoride, from dimethyl sulfate and potassium fluoride (Scheme 1.17, 1). Later in 1862, Borodin, a well-known music composer, carried out the first halogen exchange experiment for the synthesis of benzoyl fluoride from benzoyl chloride in the presence of potassium hydrogen difluoride (Scheme 1.17, 2). In 1870, the first synthesis of aryl fluoride was achieved by Schmitt and von Gehren, via thermolysis of aryl diazonium salt with hydrofluoric acid, and this result was repeated and confirmed by Lenz in 1877 (Scheme 1.17, 3). This reaction suffered from low yields due to the poor nucleophilicity of solvated fluoride ion and competing reaction from water. This problem was later addressed by Balz and Schiemann in 1927 by using a fluoroboric acid or its salts, instead of hydrofluoric acid, to synthesize aryl fluorides. This
improved method has proved to be one of the most important synthetic methods in organofluorine chemistry, and is still used in the industrial production of aromatic fluorides.

Scheme 1.17. Early developments in organofluorine chemistry.

In 1892, Swarts made the important discovery that chlorine/fluorine exchange could be effected on chlorocarbons (9) by antimony(V) dibromide trifluoride to form chlorofluorocarbons (CFCs, 29) and fluorocarbons (Scheme 1.18).\textsuperscript{96} In 1928, CFCs were discovered by Midgley to be excellent refrigerants,\textsuperscript{97} which opened up their widespread industrial application. Another significant breakthrough came when the research of CFCs serendipitously led to the discovery of polytetrafluoroethylene (PTFE) at DuPont,\textsuperscript{98} which later initiated probably the biggest industrial success of fluorine chemistry — fluoropolymers.\textsuperscript{68} Fluorocarbons and fluoropolymers were also crucial for uranium enrichment in the Manhattan Project during the World War II.\textsuperscript{99}

Scheme 1.18. Swarts’ Cl/F exchange reaction by SbF\textsubscript{3}Br\textsubscript{2} to synthesize trichlorofluorocarbon.

After the successful isolation of elemental fluorine, Moissan studied the reactions of elemental fluorine with organic molecules, but the reactions usually proceeded very vigorously and exothermally (combustion or explosion) in an uncontrollable manner.\textsuperscript{88} This feature of elemental
fluorine, together with the difficulty and expense of its production, made its future uncertain in the synthesis of organofluorine molecules. Moissan also studied the interaction of elemental fluorine with carbon in 1890 and isolated the simplest fluorocarbon molecule, carbon tetrafluoride. By dilution with inert gas, such as nitrogen, elemental fluorine can be applied to fluorination reactions in either vapor, liquid or solid phases, and this approach proved important for the syntheses of fluorocarbons.

Another two areas where organofluorine chemistry has found notable successes are pharmaceuticals and agrochemicals. In 1954, Fried pioneered the synthesis of fluorinated hydrocortisone acetate (Figure 1.8). His study showed that 9-α-fluorohydrocortisone acetate (30) has eleven-fold higher bioactivity than the parent molecule, which suggested the potential significance of fluorine on biological properties of organic molecules.

![Figure 1.7](image-url)

_Figure 1.7._ Fried’s synthesis on 9-α-fluorohydrocortisone acetate.

Fluorine, due to its small size, is considered to be a good bioisostere for hydrogen and can form a strong covalent bond, C-F. The large electronegativity of fluorine imposes strong inductive effects that strengthen the bonds of the proximate atoms in organic molecules, and therefore leads to enhanced thermal and metabolic stability. Moreover, fluorine can modulate many other physiochemical properties, such as lipophilicity, acidity, basicity, polarizability, structural
conformation, which makes fluorine advantageous and versatile in pharmaceutical and agrochemical sciences.¹⁰²⁴

1.2.3 **Fluorinating reagents for the syntheses of organofluorine compounds**

Generally, there are two approaches to incorporate fluorine substituents into organic molecules: 1) fluoroalkylation/fluoroarylation using building blocks that already have fluorine appended, and 2) fluorination to directly form F-A bonds (mostly F-C bond). This thesis will mainly focus on the second approach.

1.2.3.1 **Nucleophilic fluorinating agents**

The efficiency and success of nucleophilic fluorination with fluoride agents usually require aprotic solvent as hydrogen bonding significantly weakens the nucleophilicity of fluoride.¹⁰⁵ Anhydrous hydrogen fluoride, though effective for nucleophilic fluorination, is not practical for organic synthesis, as it is highly corrosive and has a low boiling point. Many metal fluoride salts, such as silver fluoride and alkali metal fluorides, have been used as fluoride sources, but they are often poorly soluble in organic solvents and require high temperatures to aid the solubility of ionic fluorides.⁷³,¹⁰⁶

Recently, it has been shown that transition metal catalysts are able to promote the reactions of metal fluorides through the formation of catalytic transition metal fluorides. For instance, in 2009, Buchwald and coworkers developed the first palladium-catalyzed fluorination of aryl triflates and aryl bromides to form aryl fluorides using CsF or AgF as fluoride sources (Scheme 1.19).¹⁰⁷,¹⁰⁸ It was demonstrated that this reaction involves a key [ArPd-F] complex, which leads to the aryl fluoride product through reductive elimination.
Scheme 1.19. Pd-catalyzed fluorination of aryl triflate and aryl bromide with metal fluorides.

A variety of organic salts of fluoride have been developed to help with solubility and ease of operation on anhydrous hydrogen fluoride, such as tetrabutylammonium fluoride (TBAF, 34), pyridinium fluoride (Py•9HF, PPHF, Olah’s reagent, 35), triethylamine hydrofluoric acid (Et₃N•3HF, 36), and tris(dimethylamino)-sulfonium difluorotrimethylsilicate (TASF, 37) (Figure 1.8).¹⁰⁶,¹⁰⁷

Hypervalent sulfur fluoride reagents have been applied for the conversion of C-O bonds to C-F bonds (deoxofluorination).⁷³,¹⁰⁹ Sulfur tetrafluoride (38) was the first reagent examined in this context, and can convert alcohols, ketones, aldehydes and carboxylic acids into alkyl fluorides, -difluorides and -trifluorides respectively.¹¹⁰ However, sulfur tetrafluoride requires special apparatus, because the reactions generally operate at high temperature (100-200 °C) and high pressure in stainless steel vessels. Furthermore, it is a gas with a boiling point at −40 °C, and has the toxicity (Recommended Exposure Limited: 0.4 mg/m³) similar to phosgene. These shortcomings were largely addressed with the development of diethylaminosulfur trifluoride
(DAST, 39) by Du Pont (Figure 1.9). This reagent was derived from SF₄, but is a liquid at ambient temperature and relatively easy to handle with standard laboratory equipment. It also possesses similar reactivity as SF₄ and is mainly used for the syntheses of alkyl fluorides from alcohols, and alkyl difluorides from ketones or aldehydes. However, the thermal instability has been an issue for DAST when forcing conditions were required, or on large scale. *bis*(2-Methoxyethyl)aminosulfur trifluoride (Deoxofluor, 40) has been discovered to have improved thermal stability and practicality as an alternative reagent (Figure 1.9). The sulfonium salt version of DAST was also found to show good thermal stability. Recently, another novel reagent based on sulfonyl fluoride, 2-pyridinesulfonyl fluoride (PyFluor, 42), has been demonstrated to be a chemoselective, safe, and economically viable deoxyfluorination agent. Imidazolidine-based 2,2-difluoro-1,3-dimethylimidazolidine (DFI, 41) is capable of deoxyfluorination under mild conditions, but can also be used to synthesize vinyl fluorides or alkynes from ketones, and aryl fluorides from phenol.

![Chemical Structures](image)

**Figure 1.9.** Electrophilic fluorinating agents for hydroxyl and carbonyl groups.

Other hypervalent atom-based reagents have also been developed for selective fluorination, such as xenon difluoride (43, Figure 1.10) and iodine reagents (Figure 1.10). Due to the oxidizing ability of hypervalent Xe and I, the fluorination methods with these reagents often involve oxidative processes. Some high valency metal fluorides, such as cobalt trifluoride and silver difluoride, have also been reported in fluorination reactions, as both oxidants, and fluoride or...
atomic fluorine sources, but are rarely used in organic synthesis due to the poor chemoselectivity of these reagents.\textsuperscript{116}

![Figure 1.10. Xenon difluoride and hypervalent iodine(III) reagents 44 and 45.](image)

Xenon difluoride can be prepared from the reaction of xenon gas with elemental fluorine, and is commercially available as a stable solid.\textsuperscript{117} It has been demonstrated to be one of the most useful fluorinating agent in the fluorination of alkenes, carboxylic acids, thioethers, and aromatic and aliphatic compounds (Scheme 1.20).\textsuperscript{118, 119} The mechanisms could involve nucleophilic, electrophilic or radical processes, depending on the specific transformation and conditions.

![Scheme 1.20. Organic fluorination enabled by xenon difluoride.](image)
*p*-Tolyliododifluoride (44, Figure 1.10) was found to be able to convert alkene to alkyl difluoride as early as the 1930s. In general, iodoaryl difluoride reagents are used for fluorination of alkenes and sulfur compounds. These two fluorination reactions involve a key nucleophilic substitution reaction on the electrophilic hypervalent iodine center to form iodonium 47 and sulfonium intermediates respectively. A subsequent reaction with fluoride ion affords fluorinated product 49 (Scheme 1.21). Similar monofluorination or difluorination of β-keto esters or ketones with hypervalent iodine reagents have also been reported. In addition, iodine-catalyzed difluorination of alkenes has been developed under the conditions with a stoichiometric amount of oxidant, such as *m*-chloroperbenzoic acid (*m*-CPBA), and fluoride sources, such as PPHF or Et₃N·3HF. It involves the formation of the hypervalent iodine catalytic species, (difluoroiodo)arene, *in situ* from aryl iodide, before it reacting with alkenes. The iodine catalytic system has been successfully applied to the enantioselective 1,2- or 1,1-difluorination of alkene by the use of chiral aryl iodide catalysts.

![](image)

**Scheme 1.21.** Fluorination of alkene via (difluoroiodo)arene.

### 1.2.3.2 Electrophilic fluorinating agents

Due to the large electronegativity of the fluorine atom, it is generally challenging to obtain electrophilic fluorine. The common ways to overcome this problem are to have either strong electron-withdrawing groups or excellent leaving groups bound to the fluorine atom, or the combination of these two ways. There have been many types of electrophilic fluorinating agents.
that have been, including elemental fluorine (F₂), xenon difluoride, perchloryl fluoride (FCIO₃), hypofluorite reagents (O-F) and N-F type reagents (Table 1.3).⁷³,⁷⁵

**Table 1.3.** Summary of electrophilic fluorinating agents.

<table>
<thead>
<tr>
<th>Fluorine bond</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others</td>
<td>F-F</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>O-F</td>
<td>CF₃O-F</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>N-F</td>
<td>RSO₂⁻ N⁺ SO₂⁻ R</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Molecular fluorine can react as electrophilic fluorine source at low temperatures and selectively fluorinate the most electron-rich C-H bonds for both aliphatic and aromatic substrates. For instance, molecular fluorine can achieve β-fluorination for silyl enol ether or enol acetate. Hypofluorites and related reagents can fluorinate electron-rich arenes and oxo-fluorinate alkenes.⁷³,⁸⁵

While effective in some cases of selective fluorination,⁷⁴,⁸⁵ molecular fluorine and hypofluorite reagents are difficult to use on large scale, as they are powerful oxidants, highly reactive, and toxic.⁷³ Research on developing safer and alternative reagents led to the discovery of N-F based electrophilic fluorinating agents (Table 1.3), such as N-fluoropyridinium triflate (NFPy, ⁵⁶), N-fluorobenzenesulfonylimide (NFSI, ⁵³), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, ⁵⁴) and N-fluorosultams
These reagents are mostly stable solids, safe, easy to handle, and effective in selective electrophilic fluorination. Ever since their discovery, these N-F fluorinating agents have found wide application in the fluorination of aromatics, organometallic compounds, alkenes, thioethers and carbanions. They have also been successfully utilized in enantioselective electrophilic fluorination (example with N-fluorosultam, see Scheme 1.26).

**Scheme 1.22.** The first enantioselective fluorination of enolate by N-fluorosultam (57).

For electrophilic fluorinations using N-F reagents, it has been hypothesized that two fluorination mechanisms could operate: (1) Nucleophilic substitution, (2) Single electron transfer and fluorine atom transfer (FAT) sequence (Scheme 1.23).  

1) Nucleophilic substitution on fluorine

\[
\text{Nu}^- + \text{F}-\text{X} \xrightarrow{\text{SN2}} \text{Nu}^\text{-F} + \text{X}^- 
\]

2) Single electron transfer and fluorination

\[
\text{Nu}^- + \text{F}-\text{X} \xrightarrow{\text{SET}} \text{Nu}^\bullet + \left[\text{F}-\text{X}\right]^\bullet \xrightarrow{\text{FAT}} \text{Nu}^\text{-F} + \text{X}^- 
\]

**Scheme 1.23.** Possible mechanisms for electrophilic fluorination.

In 1990, Umemoto *et al.* proposed a single electron transfer mechanism in the study of electrophilic fluorination by NFPy, and related fluorinating agents. As illustrated in Scheme 1.24, single electron transfer occurs through a $\pi$ complex formed between the substrate silyl enol ether 60 and N-fluoropyridinium salt (NFPy). A subsequent fluorine atom transfer gives the $\beta$-fluorocarbocation intermediate 61, which eventually leads to the $\beta$-fluoroketone product 62.
Differding\textsuperscript{129,130} and Wong,\textsuperscript{131} together with their coworkers, investigated the mechanism of electrophilic fluorination of enolates and enol ethers with N-F reagents, through radical cyclization and radical clock experiments respectively. However, their studies were unable to offer definite evidence for the formation of radical intermediates.

Organocatalysis and transition metal catalysis have demonstrated important applications in electrophilic fluorination, especially to achieve chemoselectivity or fluorination of challenging substrates.\textsuperscript{107,125} For instance, Ritter and coworkers recently reported a palladium-catalyzed direct aromatic C-H fluorination using Selectfluor or NFSI.\textsuperscript{132} They demonstrated that the Pd(II) catalyst was oxidized by NFSI or Selectfluor to form a key Pd(IV)-F complex, which reacts with arenes to form aryl fluorides through electrophilic aromatic fluorination (Scheme 1.25).

\textbf{Scheme 1.24.} Proposed SET mechanism for electrophilic fluorination of silyl enol ether by NFPy.

\textbf{Scheme 1.25.} Pd-catalyzed electrophilic aryl C-H fluorination using N-F reagents.
1.2.3.3 Radical fluorinating agents

*Traditional reagents for radical fluorination*

In 1937, Bigelow and Calfee were able to control the heat of molecular fluorine reactions by diluting the reagent with an inert gas, such as molecular nitrogen.\textsuperscript{133} With this approach, they were able to achieve the radical fluorination of gaseous organic molecules, such as methane and ethane. This process operates through a radical chain mechanism under either photochemical or thermal conditions.

Hypofluorites can also be used as radical fluorinating agents.\textsuperscript{74} Trifluoromethyl hypofluorite (CF$_3$OF) was prepared by Cady and Kellogg in 1948,\textsuperscript{134} and has been demonstrated to undergo fluorinations via a radical mechanism under photochemical conditions, or in the reaction with electron-poor olefins. Generally, radical fluorination by hypofluorites affords poor regio- and stereoselectivities.\textsuperscript{74}

Xenon difluoride has been demonstrated able to react with carbon radicals due to the weak F-Xe-F bonds (average Xe-F BDE = 32 kcal/mol). One of such radical fluorinations is a XeF$_2$-mediated fluorodecarboxylation (a Hunsdiecker-type reaction).\textsuperscript{118} This reaction begins with the formation of fluoroxyenon carboxylate species, which then undergoes radical fragmentation to give an alkyl radical and a fluoroxyenon radical with concomitant loss of carbon dioxide. This radical mechanism was supported by the formation of a cyclized product in intramolecular radical cyclization in the experiment by Patrick and coworkers (Scheme 1.26).\textsuperscript{135} The resultant alkyl radical is then fluorinated via either a fluorine atom transfer or SET and fluoride transfer, depending on the reaction conditions.\textsuperscript{119}
**Scheme 1.26.** Mechanism of fluorodecarboxylation of carboxylic acid via XeF₂.

*New reagents for radical fluorination*

While it has been proposed that electrophilic fluorination with N-F agents involves radical intermediates, the mechanistic studies have been either inconclusive or even contradictory. Before 2012, radical fluorination had been limited to the oxidizing agents discussed above, i.e. elemental fluorine, hypofluorites and XeF₂. In 2012, Sammis and coworkers demonstrated that electrophilic N-F reagents can also serve as sources of atomic fluorine (Figure 1.11). Specifically, they demonstrated that both NFSI and Selectfluor can react with alkyl radicals to form alkyl fluorides (Scheme 1.27). In the same year, Sammis and coworkers further applied Selectfluor to radical fluorodecarboxylations of 2-arylxy and -aryl acetic acids under UV light, in which Selectfluor is an oxidant, but also a radical fluorinating agent to react with aryloxy methyl radicals or benzyl radicals to form fluoromethyl aryl ethers or benzyl fluorides, respectively (Scheme 1.28, 1). In 2014, Sammis, Paquin, and coworkers applied a ruthenium-based visible light photoredox catalytic system to this radical fluorodecarboxylation reaction with Selectfluor for fluoromethyl aryl ether syntheses.
Figure 1.11. Proposal of fluorine atom transfer from N-F agents to carbon radical.

Scheme 1.27. NFSI used in fluorination of alkyl radical formed from photolysis or thermolysis of peresters and diacyl peroxides.

In 2012, Li and coworkers also developed the first transition metal-catalyzed radical fluorodecarboxylation with Selectfluor for the efficient syntheses of alkyl fluorides (Scheme 1.28, 2). Almost at the same time, Boger and Barker reported the first radical hydrofluorination of unactivated alkenes mediated by an Fe(III)/NaBH₄ system using Selectfluor as the radical fluorinating agent. This hydrofluorination reaction gave exclusively Markovnikov addition products (Scheme 1.28, 3). They proposed that [Fe-H] species serves as hydrogen atom donor to add into alkene at the less hindered side to form secondary or tertiary carbon radicals before fluorination by Selectfluor. Shortly afterward, Lectka and coworkers reported a polycomponent copper-catalyzed C-H radical fluorination with Selectfluor (Scheme 1.28, 4). Later, their studies demonstrated that this process involved a copper-initiated radical chain mechanism, which was propagated using a Selectfluor-derived cation radical. The same year also witnessed the breakthrough by Groves and coworkers that the nucleophilic fluorinating agent, silver(I) fluoride
was successfully applied to the radical fluorination of aliphatic C-H bonds catalyzed by manganese(III) porphyrin complex 66 (Scheme 1.28, 5).\textsuperscript{143} It was proposed that Mn(IV)-F porphyrin complex is the key intermediate to react with alkyl radicals to give the alkyl fluorides.

\begin{equation}
\begin{align*}
\text{(1)} \quad & \text{R}_1^1 \text{O} \text{COOH} & \xrightarrow{3.5 \text{ equiv Selectfluor}} & \text{R}_1^1 \text{O} \text{F} \\
& \quad & & \text{H}_2\text{O}, h\nu 300 \text{ nm}, 1 \text{ h} \\
& \quad & & \text{R}_2^2 = \text{H, F}
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{(2)} \quad & \text{R} - \text{COOH} & \xrightarrow{20 \text{ mol}\% \text{AgNO}_3, 2 \text{ equiv Selectfluor}} & \text{R} - \text{F} \\
& \quad & & \text{H}_2\text{O}/\text{Acetone (1 : 1)}, \text{reflux}, 10 \text{ h} \\
& \quad & & \text{R} = \text{alkyl}
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{(3)} \quad & \text{R}_1^1 \text{R}_2^2 \text{R}_3^3 & \xrightarrow{2 \text{ equiv Selectfluor}, 2 \text{ equiv Fe}_2(\text{ox})_3, 6.4 \text{ equiv NaBH}_4} & \text{R}_1^1 \text{R}_2^2 \text{H} \\
& \quad & & \text{MeCN/H}_2\text{O (1 : 1), 0 °C, 30 min}
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{(4)} \quad & \text{R} - \text{H} & \xrightarrow{10 \text{ mol}\% \text{CuI}, 10 \text{ mol}\% \text{BPMED}, 10 \text{ mol}\% \text{KB(C}_6\text{F}_5)_4, 10 \text{ mol}\% \text{NHPI, 2.2 equiv Selectfluor}} & \text{R} - \text{F} \\
& \quad & & 1.2 \text{ equiv KI}, \text{CH}_3\text{CN} \\
& \quad & & \text{reflux}, 2 \text{ h}
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{(5)} \quad & \text{R} - \text{H} & \xrightarrow{6-8 \text{ mol}\% \text{Mn(TMP)Cl}, 3 \text{ equiv AgF}, 8 \text{ equiv PhIO, 0.3 equiv TBAF+3H}_2\text{O}} & \text{R} - \text{F} \\
& \quad & & \text{CH}_3\text{CN/CH}_2\text{Cl}_2 (3 : 1), 50 °C}
\end{align*}
\end{equation}

**Scheme 1.28.** Representative breakthroughs on radical fluorination with N-F agents and fluorides in 2012.

1.3 Conclusions

Radical and fluorine chemistry have presented a myriad of possibilities and opportunities for the advancement of modern synthetic technologies. This is perfectly exemplified by the important innovation of radical fluorination methodologies in the syntheses of organofluorine molecules.\textsuperscript{70,72} However, modern organic synthesis still faces many kinds of challenges that significantly limit the
development of innovative pharmaceuticals. Two such challenges are the syntheses of organofluorine compounds and heterocycles, which await further innovations for the exploration of large structural diversity and high synthetic efficiency.

In the following parts of this thesis, Chapters 2 and 3 will introduce my research on fluorine chemistry. Specifically, Chapter 2 includes the development of a novel radical fluorodecarboxylation method to demonstrate the efficiency of radical reactions in the syntheses of di- and trifluoromethyl ethers, two pharmaceutically relevant motifs. Chapter 3 includes the mechanistic studies of radical fluorinations, for the purpose of acquiring further insights into the reactions between fluorinating agents and carbon radicals. Chapters 4 and 5 will introduce my research on the development of new synthetic methods of radical cyclization for the syntheses of nitrogen heterocycles, such as phthalazine and pyridazine derivatives, and other nitrogen-containing motifs, such as 1,4-diamines. These two chapters will demonstrate not only my exploration on new reactivities of hydrazones in radical cyclizations, but also the use of these methods to address the synthetic challenges of pharmaceutically relevant nitrogen heterocycles. Overall, the scientific projects I adventured with my colleagues are in the goal of providing better understanding of radical reactions and developing robust and efficient methodologies to access valuable pharmaceutically relevant organic motifs.
Chapter 2: Syntheses of Di- and Trifluoromethyl Ethers with Xenon Difluoride

Fluorine is an important component in many modern pharmaceuticals and agrochemicals due to its ability to influence the physicochemical and biological properties of organic molecules.\textsuperscript{102,103} It has been incorporated in the context of many different motifs, such as alkyl or aryl fluorides, mono-, di- and trifluoromethyl groups, 2,2,2-trifluoro- and perfluoro-ethyl groups, and a perfluoroisopropyl group.\textsuperscript{101} Although a wide variety of fluorination methods and reagents have been developed (Chapter 1, section 1.2), the exploration of diverse organofluorine motifs is still largely limited by their synthetic accessibility.\textsuperscript{71} In addition, the incorporation of \textsuperscript{18}F into organic molecules still faces various constrains due to the lack of efficient methods, as \textsuperscript{18}F, a prominent nucleus for PET, only has about a two-hour half-life.\textsuperscript{69} These challenges impose an ever-increasing demand for innovative and novel synthetic technologies that allow more facile and efficient access to diverse organofluorine motifs.\textsuperscript{104}

In the course of an industrial collaboration, the Sammis laboratory became interested in the development of new synthetic methods for the syntheses of organofluorine motifs, especially fluoromethyl ethers,\textsuperscript{144,145} which can be challenging in late-stage pharmaceutical synthesis.\textsuperscript{107,146} The overall synthetic strategy to access fluoromethyl ethers used in the research of Sammis group has been to access these motifs using a radical fluorodecarboxylation from the corresponding alkoxy- or aryloxy (fluoro)acetic acids (Scheme 2.1). Following this strategy, several methods for
mono- and di-fluoromethyl ether formation have been reported using Selectfluor or NFSI in photochemical radical fluorodecarboxylations.\textsuperscript{137,138,147}

![Scheme 2.1. Radical fluorodecarboxylation approach to access fluoromethyl ethers.]

This chapter focuses on my work towards a radical fluorodecarboxylative approach to the syntheses of di- and trifluoromethyl ethers using xenon difluoride.\textsuperscript{148} It starts with a general introduction on fluorodecarboxylation, as well as properties and synthetic approaches to di- and trifluoromethyl ethers. I will then give a brief summary of the initial work on this project, performed by my former colleagues Dr. Claire Chatalova-Sazepin and Meruyert Binayeva, followed by my contributions to the project.

### 2.1 Fluorodecarboxylation

A fluorodecarboxylation reaction is a process in which a carboxylic acid is converted to an aryl or alkyl fluoride with concomitant loss of carbon dioxide (Scheme 2.2). This transformation dates back to 1929 when Fichter and Brunner observed the formation of methanol, formaldehyde, carbon dioxide and ethylene from the reaction of molecular fluorine with aqueous potassium acetate.\textsuperscript{149} While it has been hypothesized that methyl fluoride was also formed, it was not detected, most likely due to \textit{in situ} degradation. In 1960, electrochemical conditions were applied to the fluorodecarboxylation of short-chain carboxylic acids to yield predominantly perfluoroalkanes.\textsuperscript{150} In 1969, the first selective fluorodecarboxylation method was accomplished by Grakauskas, who applied elemental fluorine to fluorodecarboxylation with aqueous alkali salts of
carboxylic acids, such as malonic, succinic, glutaric acid, or \( p \)-nitrobenzoic acid.\(^{151} \) They proposed that the fluorodecarboxylation occurred through acyl hypofluorite intermediates in an ionic fluorodecarboxylation process.

\[
\begin{align*}
\text{R-COOH} & \quad \text{Reagents} & \quad \text{R-F} + \text{CO}_2 \\
\end{align*}
\]

Scheme 2.2. Fluorodecarboxylation of carboxylic acid to form alkyl or aryl fluoride.

In 1983, Patrick \textit{et al.} reported a practical method for the fluorodecarboxylation of aliphatic acids using xenon difluoride.\(^{135} \) Subsequent mechanistic experiments indicated that the decarboxylative process first involves the formation of fluoroxenon carboxylate, which then undergoes radical decarboxylation and subsequent fluorination (Scheme 1.26).

With the discovery of stable and safe radical fluorinating agents, such as Selectfluor and NFSI,\(^{136} \) a variety of new fluorodecarboxylation methods have been developed.\(^{70} \) In 1995, Forrest \textit{et al.} reported the first Selectfluor-mediated fluorodecarboxylation as the key step in the syntheses of polyfunctionalized furans.\(^{152} \) In the same year, Scott and Wang further investigated this reaction with pyrrole substrates, and successfully applied it to the synthesis of 2-fluoroporphobilinogen (F-PBG, 69), which has the potential as an inhibitor of the enzyme porphobilinogen (PBG) deaminase (Scheme 2.3).\(^{153} \) In 2016, Selectfluor was employed again in the fluorodecarboxylation of cinnamic acids to form vinyl fluorides, though with poor stereoselectivities.\(^{154} \) In 2018, Liu and coworkers also examined these conditions for the fluorodecarboxylation of naphthalene and quinoline carboxylic acids with \textit{ortho}-hydroxyl or amino groups, and were able to synthesize a variety of aryl fluorides in good yields.\(^{155} \)
Scheme 2.3. Fluorodecarboxylation of pyrrolecarboxylic acid by Selectfluor for the synthesis of 2-fluoroporphobilinogen (F-PBG).

In spite of the successful use of N-F reagents in ionic fluorodecarboxylations, it was not until 2012 that they were first applied to radical fluorodecarboxylations. After the discovery of Selectfluor and NFSI as radical fluorinating agents by Sammis and coworkers, Li and coworkers reported the first Selectfluor-mediated fluorodecarboxylation of aliphatic carboxylic acids with a silver-catalyzed system (Scheme 1.28, 2).139 Gouverneur, Passchier, Solin, and coworkers later applied this method to the syntheses of mono $^{18}$F radiolabelled di- and trifluoromethylarenes with $[^{18}$F]Selectfluor from the corresponding mono- and difluoroarylacetic acids (Scheme 2.4).156 In 2017, Li and coworkers applied their own method to the fluorine incorporation of poly(meth)acrylic acids to synthesize poly(vinyl fluoride-co-acrylic acid) and poly(2-fluoropropene-co-methacrylic acid copolymers.157 Several heterogeneous silver catalysts have also shown promising results for radical fluorodecarboxylations, such as a Ag$_2$O/TiO$_2$ catalyst158 and a AgFeO$_2$ nanoparticle catalyst.159

Scheme 2.4. $[^{18}$F]F-radiolabeling for tri- and difluoromethylarenes via silver catalyzed-radical fluorodecarboxylation with $[^{18}$F]Selectfluor.
In 2012, Leung, Chatalova-Sazepin, et al. in the Sammis laboratory developed a photochemical radical fluorodecarboxylation of α-aryloxy and -aryl acetic acids under ultraviolet (UV) light using Selectfluor as the oxidizing and fluorinating agent. This method can access mono- and difluoromethyl aryl ethers, as well as benzyl fluorides (Scheme 2.5, 1). Shortly after, Leung et al. applied NFSI towards photosensitized radical fluorodecarboxylations using acetone or benzophenone (Scheme 2.5, 2).

\[
\begin{align*}
(1) & & \text{R}^1\text{CO}_2\text{H} & \xrightarrow{3.5 \text{ equiv Selectfluor} \atop 1.5 \text{ equiv NaOH}} & \text{R}^1\text{F} \\
R^1 = \text{ArO, Ph} & & \text{R}^2 = \text{H, F, OAc} & & \text{H}_2\text{O, h} \nu \text{ 300 nm, 1 h}
\end{align*}
\]

Selected examples:

\[
\begin{align*}
72 & & \text{60\% (94\%)} \\
73 & & \text{78\%} \\
74 & & \text{72\% (> 95\%)} \\
75 & & \text{64\%a}
\end{align*}
\]

\[
\begin{align*}
(2) & & \text{ArO}\text{CO}_2\text{H} & \xrightarrow{4.0 \text{ equiv NFSI} \atop 0.5 \text{ equiv base}} & \text{ArO}\text{F} \\
\text{acetone, h} \nu \text{ 300 nm}
\end{align*}
\]

Selected examples:

\[
\begin{align*}
76 & & \text{ (> 95\%)} \\
77 & & \text{66\%} \\
78 & & \text{73\%} \\
79 & & \text{49\%}
\end{align*}
\]

Yields in parentheses are determined by $^1$F NMR spectroscopy

**Scheme 2.5.** Selectfluor- or NFSI-mediated photo-fluorodecarboxylation.

In 2014, Paquin, Sammis and coworkers reported the first photoredox catalytic radical fluorodecarboxylation, using [Ru(bpy)_3]Cl_2 and Selectfluor. In this method, a SET process occurs between the photoexcited Ru(II) species and Selectfluor to generate the Ru(III) catalytic
species, which is the key oxidant to enable the subsequent radical decarboxylative fluorinations of carboxylate intermediates. The mild conditions and use of visible light instead of UV light demonstrated improved practicality for the syntheses of fluoromethyl aryl ethers (Scheme 2.6, 1).

\[
\text{(1)} \quad \text{ArO} \text{CO}_2\text{H} \quad \underset{\text{1 mol% [Ru(bpy)]_3Cl}_2 \atop 3.5 \text{ equiv Selectfluor} \atop 1.5 \text{ equiv NaOH}}{\text{CH}_3\text{CN}/\text{H}_2\text{O (1 : 1)}} \quad \underset{\text{500 W lamp, 1 h}}{\text{ArO} \text{F}}
\]

\[
\text{(2)} \quad \text{R} \text{CO}_2\text{H} \quad \underset{\text{1 mol% (Ir[dF(CF}_3\text{ppy})_2(dtbpy)]PF}_6 \atop 3.0 \text{ equiv Selectfluor} \atop 2 \text{ equiv Na}_2\text{HPO}_4}{\text{CH}_3\text{CN}/\text{H}_2\text{O (1 : 1), 23 °C, 6 h}} \quad \underset{\text{34 W blue LEDs}}{\text{R} \text{F}}
\]

\[
\text{(3)} \quad \text{R} \text{CO}_2\text{H} \quad \underset{\text{5 mol% Mes-AcrClO}_4 \atop 2.0 \text{ equiv Selectfluor} \atop 1.0 \text{ equiv Cs}_2\text{CO}_3}{\text{CH}_3\text{CN}/\text{H}_2\text{O (1 : 1), rt}} \quad \underset{\text{23 W CFL}}{\text{R} \text{F}}
\]

**Scheme 2.6.** Photoredox catalytic radical fluorodecarboxylation of aliphatic carboxylic acids.

In 2015, MacMillan and coworkers reported an iridium-catalyzed photoredox radical fluorodecarboxylation of aliphatic carboxylic acids using Selectfluor (Scheme 2.6, 2).\(^{160}\) This method involves a oxidative quenching process for the photoexcited Ir(III) catalyst to form an Ir(IV) species via oxidation by Selectfluor, before the radical decarboxylative fluorination occurs. In the same year, Ye and coworkers reported the acridinium-based photoredox catalytic radical fluorodecarboxylation of aliphatic acids, also using Selectfluor.\(^{161}\) In contrary to previous transition metal photoredox catalytic methods, a reductive quenching process was involved, as the
photoexcited organocatalyst effects the radical decarboxylation directly. Both of the methods by MacMillan and Ye demonstrated good compatibility for the syntheses of various alkyl fluorides.

Groves and coworkers have recently demonstrated that nucleophilic fluorinating agents, such as fluoride, are viable for radical fluorodecarboxylation reactions. Following their initial report on oxidative C–H fluorination via manganese catalysis (Scheme 1.31, 4), Groves and coworkers reported that the same Mn-porphyrin catalytic system can successfully effect fluorodecarboxylation of aliphatic carboxylic acids using triethylamine trihydrofluoride as the fluoride source (Scheme 2.7). They suggested that the carboxylic acid is most likely to form an iodine(III) carboxylate ester first, which oxidizes the Mn(III)-porphyrin catalyst to form a Mn(IV) species and to effect the radical decarboxylation concurrently. The alkyl radical was further fluorinated by a Mn(IV)-F species. The potential of this method for PET imaging was also demonstrated by the 18F-radiolabelling of a variety of carboxylic acids with non-carrier-added [18F]fluoride in 20% to 50% radiochemical conversions.

\[
\text{R-CO}_2\text{H} \xrightarrow{2.5 \text{ mol\% [Mn(TM)]Cl, 3.3 equiv PhIO, 1.2 equiv Et}_3\text{N•3HF, DCE, 45 °C, 45 min - 1.5 h}} \text{R-F}
\]

Selected 18F labelled products in conditions: [18F]fluoride, CH₃CN, 50 °C, 10 min
n is the number of repeats

<p>| | | | |</p>
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<tr>
<td>82</td>
<td>50% ± 3% (n = 4)</td>
<td>83</td>
<td>38% ± 10% (n = 6)</td>
</tr>
<tr>
<td>84</td>
<td>40% ± 4% (n = 3)</td>
<td>85</td>
<td>26% ± 2% (n = 2)</td>
</tr>
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Scheme 2.7. Mn-catalyzed radical fluorodecarboxylation of aliphatic carboxylic acids using nucleophilic fluorinating agent and its application in 18F-F-radiolabelling.
2.2 General aspects of di- and trifluoromethyl ethers

2.2.1 Properties of di- and trifluoromethyl ethers

Fluoromethyl ethers, especially fluoromethyl aryl ethers, have drawn increasing interest in the agrochemical, pharmaceutical and material sciences (Figure 2.1).\textsuperscript{144,145} They can be used as bioisosteres for methoxy or hydroxyl groups to tune the structural and electronic properties, while providing increased metabolic stability and bioavailability to drug molecules.\textsuperscript{101,144}

The impact of fluorine on methyl ether moieties has been quantitatively studied by the successive replacement of hydrogen by fluorine in anisole’s methyl group. In the lipophilicity studies of small-molecule drugs with fluoromethyl ethers motifs, a progressive but nonlinear increase was observed on both the calculated partition coefficients (cLog $P$) and the distribution coefficients (Log $D$) of the drug molecules from OCH$_3$ to OCH$_2$F, OCHF$_2$ and OCF$_3$, which suggests an increase in lipophilicity in the same order.\textsuperscript{163} Difluoromethyl can be used as a lipophilic

\textbf{Figure 2.1.} Representative examples of bioactive molecules with tri- and difluoromethyl ether motifs.
hydrogen donor similar to hydroxyl group, with two fluorine atoms surrogating the oxygen lone pairs. Di- and trifluoromethoxy substituents also result in unexpected conformational changes, compared to the methoxy group. Trifluoromethyl phenyl ether (Ar-OCF₃) preferentially adopts a 90° C-C-O-C dihedral angle (Figure 2.2). This conformation is likely stabilized by a favorable hyperconjugative interaction of the oxygen lone pairs with the σ*C-F, and hyperconjugation of aromatic ring with the σ*O-C bond. Although difluoromethyl phenyl ether (Ar-OCHF₂) did not reveal strong preference for specific conformation, a survey of their crystal structures showed that the C-C-O-C dihedral angle for some cases is close to 90°, and fluorine atoms prefer to adopt exo-endo or endo-endo arrangements (Figure 2.2).

\[ \text{Ph-OCF}_3 \quad \equiv \quad \text{Ph-OCF}_3 \quad \equiv \quad \text{Ph-OCHF}_2 \]

**Figure 2.2.** Conformation of di- and trifluoromethyl phenyl ethers.

### 2.2.2 Methods for the syntheses of di- and trifluoromethyl ethers

A variety of methods have been developed to synthesize di- and trifluoromethyl ethers. Generally, the synthetic approaches include a carbofunctionalization/fluorination sequence, direct di- and trifluoromethylation, or di- and trifluoromethoxylation. Each of these strategies will be briefly reviewed in the subsequent sections, with an emphasis on recent advancements.
2.2.2.1 Carbofunctionalization/fluorination sequence

A carbofunctionalization/fluorination sequence involves the reaction of oxygenated nucleophiles, i.e. phenols or alcohols, with carbon-based reagents to form C-O bonds, which are subsequently fluorinated at the carbon centers. Trichloromethyl ethers $^{93}$, chlorothionoformates $^{94,166}$, fluoroformates $^{95,167}$ and xanthates $^{96}$ $^{168}$ are the most common intermediates for the carbofunctionalization step (Scheme 2.8). $^{146,169}$ This strategy was pioneered by Yagupol'skii in 1955, who chlorinated anisoles with chlorine gas, followed by a halex reaction with hydrofluoric acid. $^{165}$ Although many different subsequent versions of this strategy have been developed using different reagents and conditions, they generally require harsh conditions and reagents, such as high temperature, corrosive Lewis acids, toxic and volatile reagents, and low functional group tolerance. $^{108,146}$

Scheme 2.8. Representative examples of carbofunctionalization/fluorination strategies.
Direct di- and trifluoromethylation

Nucleophilic di- and trifluoromethylation of oxygenated nucleophiles, such as phenols and alcohols, generally use different approaches; difluoromethylation are typically achieved through nucleophilic additions to a difluorocarbene,\textsuperscript{170,171} and trifluoromethylation are achieved through nucleophilic substitution with electrophilic trifluoromethylating agents (Scheme 2.9),\textsuperscript{107} though recently electrophilic difluoromethyl sources have been developed for direct nucleophilic substitution reaction by alcohols.\textsuperscript{172,173} In addition, oxidative cross coupling approach has been explored recently for di- and trifluoromethylation through the reactions between oxygenated nucleophiles with nucleophilic di- and trifluoromethyl sources.\textsuperscript{174,175}

Scheme 2.9. General approaches for tri- and difluoromethylation of oxygenated nucleophiles.

**Difluoromethylation**

Difluoromethylation of oxygenated nucleophiles traditionally utilizes CHF\textsubscript{2}X reagents. These reagents undergo a kinetically-favored deprotonation/\(\alpha\)-elimination sequence under basic conditions to form an electrophilic difluorocarbene,\textsuperscript{176,177} which is the active species for the syntheses of difluoromethyl ethers. This approach was first reported in 1910 by Swarts in his study of fluoromethane derivatives.\textsuperscript{178} He proposed the formation of a difluoromethyl ethyl ether when an alcoholic solution of difluorobromomethane (CHBrF\textsubscript{2}) was treated with potassium ethoxide. This result was repeated and confirmed four decades later by Smook and Henne in their study of fluorinated aliphatic ethers.\textsuperscript{179} In 1955, Clark and Simons explored the synthesis of difluoromethyl phenyl ether by subjecting dibromodifluoromethane (CBr\textsubscript{2}F\textsubscript{2}) to a basic solution of potassium
180 In 1960, Miller et al. examined the use of the difluorocarbene precursor, chlorodifluoromethane (CHClF₂), for the syntheses of a series of difluoromethyl aryl ethers. The difluorocarbene is formed via deprotonation/α-elimination under the reaction conditions with an excess of sodium hydroxide. The aryloxide then adds to the electrophilic difluorocarbene to form aryloxydifluoromethyl carbanion before protonation produces the difluoromethyl aryl ether (Scheme 2.10).

Scheme 2.10. Proposed mechanism for difluoromethylation of phenols via a difluorocarbene intermediate.

A variety of compounds have been discovered and developed as precursors for difluorocarbene (Figure 2.3). The first class of reagents are halomethane derivatives (CHBrF₂, CBr₃F₂, CHClF₂). Many of these reagents are toxic, and the most commonly-used CHClF₂ is also an ozone-depleting gas. In 2013, Dolbier Jr. and a worker found fluoroform, a non-ozone-depleting, nontoxic and inexpensive gas, to be a good replacement for other halomethane-based precursors of difluorocarbene, and was viable for the syntheses of difluoromethyl aryl ethers and thioethers under basic conditions.
The second class of the difluorocarbene precursors use non-halide leaving groups, such as triflate, amine and fluorosulfone. Among these three reagents, fluorosulfonyldifluoroacetic acid (100) was the first to be reported in 1989 by Chen et al. as the precursor for difluorocarbene (Scheme 2.11, 1).\textsuperscript{183} Their method does not require base, and is able to access both alkyl and aryl difluoromethyl ethers in decent yields. In 2011, Hu and coworkers discovered difluoromethyltri(n-butyl)ammonium chloride (99) as a difluorocarbene precursor, with tributylamine as the leaving group.\textsuperscript{184} In their method for the syntheses of aryl difluoromethyl ethers, only a slight excess of both sodium hydride and the reagent were needed to achieve moderate to good yields (Scheme 2.11, 2). CHF\textsubscript{2}OTf (98) was developed by Hartwig and Fier in 2013, and showed very good efficiency in the syntheses of aryl difluoromethyl ethers, with the reactions able to complete within minutes (Scheme 2.11, 3).\textsuperscript{185}
Scheme 2.11. Difluorocarbene precursors with non-halide leaving groups for the syntheses of difluoromethyl ethers.

The third class of difluorocarbene precursors consist of halide leaving groups and non-hydrogen carbanion precursors, such as carboxylate/carboxylic acid, a phenylsulfonyl group, a benzoyl group, a phosphonate, or a silyl group. Strong bases such as KOH and NaOH are usually used in large excess in reactions with these reagents to access the key difluorocarbene intermediate. In 2017, Fu and coworkers developed a novel set of conditions using visible-light photoredox catalysis to form difluorocarbene from bromodifluoroacetic acid (103) for the syntheses of difluoromethyl aryl ethers and thioethers (Scheme 2.12). This method not only demonstrated great functional group tolerance, but also used a mild base.

Scheme 2.12. Syntheses of difluoromethyl aryl ethers with bromodifluoroacetic acid using photoredox catalysis.
Scheme 2.13. TMSCF$_2$Br used for the syntheses of alkyl difluoromethyl ethers under mild conditions.

In 2017, Hu and coworkers developed a new method for the syntheses of difluoromethyl alkyl ether with TMSCF$_2$Br (107),$^{187}$ a new difluorocarbene precursor that they previously developed and applied to the syntheses of difluoromethyl aryl ethers or thioethers.$^{188}$ Their studies showed that additives like potassium acetate (KOAc) and potassium hydrogen difluoride (KHF$_2$) are as effective as, if not better than, sodium hydroxide (NaOH) in the reactions with TMSCF$_2$Br (Scheme 2.13). This method exhibits excellent compatibility with various primary, secondary and tertiary alcohols, diverse functional groups.$^{187}$

The fourth class of difluorocarbene precursors are transition metal trifluoromethyl reagents, such as Hg(CF$_3$)$_2$ (108) and ZnBrCF$_3$ (109).$^{170,189}$ They can form the difluorocarbene via an $\alpha$-elimination with concomitant formation of metal fluorides. Although bases are not needed with these reagents, the methods using these reagents for the syntheses of difluoromethyl ethers typically have very limited substrate scopes. These reagents are typically prepared from
fluoromethane derivatives, which, as mentioned above, involve significant toxicity and ecological drawbacks.

While direct nucleophilic substitution has been proposed as an approach to difluoromethyl ethers more than half a century ago, kinetic and mechanistic studies have always suggested it to be unfavorable compared to difluorocarbene formation. However, there have been great advances made by Prakash et al. in 2011 and Shen and coworkers in 2016 in the development of new reagents for direct electrophilic difluoromethylation. Prakash et al. discovered the reagent, \( N,N\text{-dimethyl-S-difluoromethyl-S-phenylsulfoximinium tetrafluoroborate (118)} \), which needs to be prepared \textit{in situ} from the corresponding sulfoximine via methylation (Scheme 2.14). Unfortunately, due to the instability of this reagent, a large excess of the alcohol (ten equivalents) was needed for the formation of difluoromethyl ethers. Shen and coworkers designed a new sulfonium ylide-based reagent, difluoromethyl-(4-nitrophenyl)-\textit{bis-(carbomethoxy)-methylide sulfonium ylide (119)}, which has improved electrophilicity and stability. This reagent demonstrated great functional group tolerance (Scheme 2.14).

\[
\begin{align*}
\text{Scheme 2.14. Electrophilic difluoromethylating reagents and direct difluoromethylation with 119.}
\end{align*}
\]

\textit{Trifluoromethylation}
The first example of a direct trifluoromethylation was reported in 2007 by Umemoto et al.,\textsuperscript{190} who studied the reactions of 2-tert-butyl-O-(trifluoromethyl)dibenzofuranium hexafluoroantimonate (121) and its analogues with alcohols and phenols to form alkyl and aryl trifluoromethyl ethers, respectively. These reagents are thermally unstable and need to be prepared \textit{in situ} by photochemical decomposition of diazonium salts at low temperature before the subsequent trifluoromethylation (Scheme 2.15). This drawback renders this approach unpractical on scale.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme2_15.png}
\caption{Syntheses of aryl and alkyl trifluoromethyl ethers via \textit{in situ} formed Umemoto reagent 121.}
\end{figure}

In 2008, Togni and coworkers demonstrated that the hypervalent iodine-based electrophilic trifluoromethylating reagents (Figure 2.4)\textsuperscript{191} they developed previously can react with phenol substrates without the need of base due to the formation of 2-iodo-benzoate in the reactions. However, poor chemoselectivity was observed in the reaction with 2,4,6-trimethyl phenol (124) (Scheme 2.16, 1).\textsuperscript{192} A subsequent discovery by Togni and coworkers unveiled the reactivity of Togni’s reagent II (123) toward triflate ion in the presence of zinc(II) triflate, and led to the application of reagent II together with zinc(II) \textit{bis}(trifluoromethylsulfonyl)imide to the syntheses of alkyl trifluoromethyl ethers (Scheme 2.16, 2).\textsuperscript{193}
Figure 2.4. Hypervalent iodine-based electrophilic trifluoromethylating reagents developed by Togni and coworkers.

Scheme 2.16. Trifluoromethylation of phenol and alcohol with Togni’s reagent II.

In 2015, Qing and coworkers successfully developed an oxidative cross coupling approach for the trifluoromethylation of oxygenated nucleophiles using TMSCF₃ and silver triflate. Many of the reagents, including the silver salt, TMSCF₃, 2-fluoropyridine and CsF, were required in large excess in the reactions (Scheme 2.17 and 2.18). Qing and coworkers demonstrated that Ag(I)CF₃ is the key species formed first from TMSCF₃ and silver triflate. It was proposed that Ag(I)CF₃ was oxidized to form a Ag(III)CF₃ species bonded with the oxygenated nucleophile, followed by reductive elimination to afford the trifluoromethyl ethers. These methods proved versatile and compatible with many different functional groups for both phenol and alcohol substrates, even for natural products and bioactive molecules, demonstrating great potential for late-stage trifluoromethylation.
2.2.2.3 Direct di- and trifluoromethoxilation

Direct di- and trifluoromethoxilation are an attractive approach to install the OCF$_3$ and OCF$_2$H moieties directly onto organic molecules. This is especially the case in the context of drug discovery as di- and trifluoromethoxilation could be executed on the same starting materials as...
those for divergent syntheses of analogues via the functionalization of organohalide, -boron, -metallic compounds, or alkenes, alkynes, carboxylic acids, or even C-H bonds.

Initial studies on direct trifluoromethoxylation date back to the work on trifluoromethyl hypofluorite (CF$_3$OF) by Cady and Porter in 1958. They synthesized perfluoro-(methyl cyclopentyl ether) (134) via the gaseous reaction between CF$_3$OF and perfluorocyclopentene (133) (Scheme 2.19). Cady and Allison subsequently demonstrated that under UV light, CF$_3$OF can also react with ethene and cyclopropane to form trifluoromethyl 2-fluoroethyl ether and trifluoromethyl 3-fluoropropyl ether respectively. However, the reaction with benzene only produced a small amount of fluorobenzene, and another fluorinated compound which was postulated to be trifluoromethyl phenyl ether based on IR spectroscopic data. It was known that CF$_3$OF could react as an electrophilic fluorine source which agrees with the cationic mechanism proposed by Barton et al. for the fluorotrifluoromethoxylation of stilbenes. However, the studies by DesMarteau and Johri on the reactions of CF$_3$OF with simple alkenes showed opposite regioselectivity which suggested a radical addition mechanism with trifluoromethoxy radical as the active intermediate. The vigorous reaction conditions and hazards associated with the use of CF$_3$OF, which by itself is potentially explosive and very toxic, necessitated the development of new direct trifluoromethoxylation methods.

Scheme 2.19. The synthesis of perfluoro-(methyl cyclopentyl ether) by Cady and Porter.
Trifluoromethoxide has emerged as a versatile intermediate for direct trifluoromethoxylation via either nucleophilic substitution or oxidative coupling. However, the intrinsic problems of the trifluoromethoxide are its weak nucleophilicity and ease of decomposition into fluoride and fluorophosgene, a highly toxic gas (Scheme 2.20). Extensive studies by Redwood and Willis have found that the equilibrium can be affected significantly by the charge/size ratio of the metal cations and cesium ion is able to favor the trifluoromethoxide formation. Further studies also showed that large-sized organic counter cations, such as tetramethylammonium and tris(dimethylamino)sulfonium, can promote the stability and nucleophilicity of the trifluoromethoxide ion in solution so that it can react with benzyl bromides or allyl bromides. However, the preparation of these trifluoromethoxide salts requires the use of fluorophosgene.

\[
\text{COF}_2 + \text{MF} \rightleftharpoons \text{M}^+ \text{OCF}_3
\]

**Scheme 2.20.** The equilibrium of trifluoromethoxide ion and fluorophosgene

Several reagents have been developed as useful trifluoromethoxide precursors (Figure 2.5). All of them can be converted to trifluoromethoxide via reactions with nucleophiles, such as fluoride. Traditionally, the *in situ* generated trifluoromethoxide from these reagents, especially TFMT (135) and 136, was mainly used for S_N2 or S_NAr reactions, and is only applicable to substrates with appropriate leaving groups or electron-deficient arenes.

![Figure 2.5. Trifluoromethoxide precursors.](image_url)
A few systems using transition metals have been developed and demonstrated distinctive capabilities for the syntheses of trifluoromethyl ethers. For instance, Ritter and coworkers, in 2010, developed a silver-mediated oxidative cross coupling reaction for the syntheses of trifluoromethyl ethers from organometallic substrates, such as arylstannanes or arylboronic acids, and a trifluoromethoxide salt 141 (Scheme 2.21, 1). Though an excess amount of silver salt and oxidant was required, this method showed good compatibility with aromatic rings of different electronics, especially electron-rich rings that are challenging to access through SnAr processes. In 2016, Zhang and coworkers developed another silver-mediated trifluoromethoxylation of α-diazo esters, in which silver(I) salt is a Lewis acid that activates the substrate to form organosilver α-diazonium ester intermediate before nucleophilic substitution by trifluoromethoxide (Scheme 2.21, 2).

Scheme 2.21. Silver-mediated trifluoromethoxylation reactions.
Scheme 2.22. Transition metal-catalyzed oxidative trifluoromethoxylation.

In 2015, Liu and coworkers reported the first transition-metal catalyzed aminotrifluoromethoxylation of alkenes using a palladium catalyst for the syntheses of 3-trifluoromethoxyoxypiperidines 143.\(^\text{203}\) It was proposed that the alkylpalladium(II) species formed via intramolecular insertion into the alkene, was oxidized by Selectfluor to form a high-valent Pd(IV)-OCF\(_3\) complex, which favors reductive elimination over \(\beta\)-fluoride elimination (Scheme 2.22, 1). Subsequently, they also developed a palladium-catalyzed direct allylic C-H oxidative trifluoromethoxylation (Scheme 2.22, 2).\(^\text{204}\) However, in this method, it was proposed that trifluoromethoxide underwent a nucleophilic substitution on an allylpalladium(II) species to form...
the trifluoromethyl ether product. These two reactions generally require a large excess of both trifluoromethoxide salts. In a different approach for alkene trifluoromethoxylation, Tang and coworkers utilized trifluoromethyl aryl sulfonate 137 as a new trifluoromethoxide source for an asymmetric silver-catalyzed bromotrifluoromethoxylation of alkenes (Scheme 2.22, 3). In this method, AgOCF$_3$ was generated *in situ* from 137 and then underwent nucleophilic reaction with a bromonium intermediate which was formed from an electrophilic bromine source and the alkene. This method afforded good to excellent diastereo- and enantioselectivities through the use of dimeric cinchona alkaloid as the chiral ligand. In 2018, they applied silver-catalyzed radical process to the direct benzyl C-H trifluoromethoxylation with 137 (Scheme 2.22, 4). It was proposed in their report that a Ag(I) catalytic species firstly reacts with 137 and an oxidant to form a FAg(II)OCF$_3$ species, which further reacted with a benzylic C-H bond to form a benzylic radical. This benzylic radical can be converted to a trifluoromethyl benzyl ether through the reaction with another FAg(II)OCF$_3$ species, or be oxidized to form a benzylic carbocation before being trapped by trifluoromethoxide.

Direct functional group activation/conversion has been another creative approach to incorporate trifluoromethoxy groups into either alkyl or aryl substrates. Tang and coworkers realized the possibility of using trifluoromethyl arylsulfonate 138 as not only a trifluoromethoxide source, but also an activating reagent in a dehydroxytrifluoromethoxylation of alcohols (Scheme 2.23, 1). Using a similar strategy, Hartwig and Zhang applied trifluoromethyl triflate to the syntheses of 2-trifluoromethoxyheterocycles from heterocyclic N-oxide via an *in situ* activation and SNAr sequence.
Reactive intermediates, such as arynes or cations, have also been utilized for trifluoromethoxylation. In 2014, Ngai and coworkers designed a novel approach for the syntheses of aryl trifluoromethyl ethers, which starts with the electrophilic trifluoromethylation of $N$-OH of the substrates $148$ by Togni’s reagent II $123$ followed by trifluoromethoxide migration to form the product through an ion pair of nitrenium and trifluoromethoxide (Scheme 2.23, 2).\textsuperscript{209} In 2018, Hu and coworkers made use of the intrinsically high reactivity of arynes for the reactions with a newly developed trifluoromethoxide precursor, trifluoromethyl benzoate ($139$), to synthesize aryl trifluoromethyl ethers (Scheme 2.23, 3).\textsuperscript{210} This method can easily access 1,2-halotrifluoromethoxylated arenes by using electrophilic halogen reagents, such as phenylethynyl bromide (for Br$^+$), perfluoroalkyl or -aryl bromides and iodides (for Br$^+$ and I$^+$), and carbon tetrachloride (for Cl$^+$).

\begin{equation}
R - \text{OH} + \begin{array}{c}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\end{array}
\begin{array}{c}
\text{OCF}_3
\end{array} \\
\begin{array}{c}
\text{OTf}
\end{array}
\begin{array}{c}
\text{TMS}
\end{array}
\begin{array}{c}
\text{R} = \text{alkyl}
\end{array}
\begin{array}{c}
\text{R} = 3 \text{ equiv}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{R}^1
\end{array}
\begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{R}^2
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{OH}
\end{array} \\
\begin{array}{c}
\text{DCM, rt}
\end{array}
\begin{array}{c}
\text{R} = \text{alkyl}
\end{array}
\begin{array}{c}
\text{R}^1 = \text{alkyl}
\end{array}
\begin{array}{c}
\text{R}^2 = \text{alkyl}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{R}^1
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{OCF}_3
\end{array} \\
\begin{array}{c}
\text{X}
\end{array}
\begin{array}{c}
\text{OTf}
\end{array}
\begin{array}{c}
\text{TMS}
\end{array}
\begin{array}{c}
\text{R} = \text{alkyl}
\end{array}
\begin{array}{c}
\text{R} = 3 \text{ equiv}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{R}^1
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{OCF}_3
\end{array} \\
\begin{array}{c}
\text{X}
\end{array}
\begin{array}{c}
\text{OTf}
\end{array}
\begin{array}{c}
\text{TMS}
\end{array}
\begin{array}{c}
\text{R} = \text{alkyl}
\end{array}
\begin{array}{c}
\text{R} = 3 \text{ equiv}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{R}^1
\end{array}
\begin{array}{c}
\text{N}
\end{array}
\begin{array}{c}
\text{OCF}_3
\end{array} \\
\begin{array}{c}
\text{X}
\end{array}
\begin{array}{c}
\text{OTf}
\end{array}
\begin{array}{c}
\text{TMS}
\end{array}
\begin{array}{c}
\text{R} = \text{alkyl}
\end{array}
\begin{array}{c}
\text{R} = 3 \text{ equiv}
\end{array}
\end{equation}

Scheme 2.23. Functional group-dependent trifluoromethoxylation for the syntheses of alkyl and aryl trifluoromethyl ethers.
In 2012, Navarrini and coworkers demonstrated the potential of using trifluoromethoxy radical in the direct synthesis of trifluoromethoxy arenes. The trifluoromethoxy radical was generated from CF₃OF under thermal or photochemical conditions, and subsequently reacted with arenes. In 2018, Ngai and coworkers developed a photoactive reagent, N-trifluoromethoxybenzoimidazole derivative 153, which can generate a trifluoromethoxy radical under photoredox conditions to functionalize arenes and heteroarenes effectively (Scheme 2.24, 1). This reaction uses mild conditions, but requires a large excess of arenes. Shortly after, they developed a redox-active reagent, N-trifluoromethoxy-N'-methylbenzotriazolium salt 154, for the same transformation (Scheme 2.24, 2). Almost at the same time, Togni and coworkers developed a new class of redox-active radical trifluoromethoxylating agents based on N-trifluoromethoxypyridinium salts, which can be readily synthesized from pyridine N-oxides and Togni reagent I 122. Under visible light conditions with a photoredox catalyst, the N-
trifluoromethoxypyridinium reagent 155 is effective for the trifluoromethoxylation of a diverse scope of arenes (Scheme 2.24, 3).

2.3 Previous work on the syntheses of di- and trifluoromethyl ethers in the Sammis laboratory

In 2012, Dr. Joe C. T. Leung and Dr. Claire Chatalova-Sazepin et al. developed a radical fluorodecarboxylation of 2-aryloxy carboxylic acids under UV light (Scheme 2.5, 1).137 It was also demonstrated that difluoromethyl aryl ethers can be synthesized in good yields from 2-aryloxy fluoroacetic acids by this method. Later in a collaboration with the Paquin group, Dr. Montserrat Rueda-Becerril et al. demonstrated the application of photoredox catalysis for the syntheses of aryl fluoromethyl ethers via radical fluorodecarboxylation (Scheme 2.6, 1).138

Dr. Claire Chatalova-Sazepin continued to explore the application of radical fluorodecarboxylation of 2-aryl difluoroacetic acids 156 to access aryl trifluoromethyl ethers 157 (Scheme 2.25). The extensive studies by Dr. Claire Chatalova-Sazepin indicated that it was challenging to achieve this oxidative radical fluorination process. It was proposed that the success of this process is essentially dependent on two fundamental steps: oxidation of carboxylic acid (or carboxylate) and radical fluorination of aryloxy difluoromethyl radical 158 by fluorine atom transfer (FAT) (Scheme 2.26). Under photochemical conditions, Selectfluor or NFSI could effect the oxidative decarboxylation of acid 156 in the excited state. However, the poor stability of the resultant carbon radical 158 required fast fluorine atom transfer. It was hypothesized that the rate of fluorine transfer from Selectfluor and NFSI were insufficient. Therefore, new reagents or reaction conditions were needed to achieve this process.
After examining the properties of alternative commercially available fluorinating reagents, Dr. Claire Chatalova-Sazepin considered xenon difluoride as a potential reagent for this radical fluorodecarboxylation. Because, compared to Selectfluor and NFSI, the high electrochemical potential of XeF$_2$ may be advantageous for the oxidation of difluorocarboxylic acids (Figure 2.6), and the two weak Xe-F bonds (BDE = 32 kcal/mol) may make XeF$_2$ an excellent fluorine donor in the FAT step (Table 1.1).

The initial test with xenon difluoride by Dr. Claire Chatalova-Sazepin afforded a moderate yield of desired product, according to the analysis by $^{19}$F NMR spectroscopy. Reaction optimization led to the development of mild conditions for the syntheses of aryl trifluoromethyl ethers.
ethers in high yields within five minutes (Scheme 2.27). Then Dr. Claire Chatalova-Sazepin and Meruyert Binayeva applied this method to the syntheses of a variety of aryl trifluoromethyl ethers with different functional groups.

Scheme 2.27. XeF₂-mediated radical fluorodecarboxylation for the syntheses of aryl trifluoromethyl ethers.

The reaction was proposed to operate via radical intermediates. This proposal was supported by the observation that reactions work better in polypropylene reaction vessels compared to borosilicate glass vessels. Borosilicate surfaces can be a good Lewis acid for electrophilic reactions of XeF₂, but is rather suppressive for XeF₂-mediated radical fluorodecarboxylations. Furthermore, a product resulting from hydrodecarboxylation was observed in chloroform, but its formation was mostly inhibited in deuterated chloroform. The reaction proceeds first with the formation of a fluoroxyenon carboxylate 159 from the carboxylic acid 156 and xenon difluoride (Scheme 2.28). A subsequent radical decarboxylation after the homolysis of Xe-O bond affords the arylxy difluoromethyl radical 158, which undergoes FAT to give the desired product.

Scheme 2.28. Proposed mechanism for XeF₂-mediated fluorodecarboxylation of 2-aryloxy difluoroacetic acid.
At this point, I joined this project to further explore xenon difluoride-mediated fluorodecarboxylation for the syntheses of aryl difluoromethyl ethers and alkyl trifluoromethyl ethers.

2.4 Results and discussion

2.4.1 Exploration of the syntheses of aryl difluoromethyl ethers

The syntheses of difluoromethyl ethers require the use of aryloxy fluoroacetic acids as substrates for the xenon-mediated fluorodecarboxylation. Following the procedure optimized by Dr. Claire Chatalova-Sazepin, aryl fluoroacetic acids 164a–c were synthesized from the corresponding phenols and ethyl 2-bromo-2-fluoroacetate (162) (Scheme 2.29).

Scheme 2.29. Syntheses of aryloxy fluoroacetic acids.

2-(4-Bromophenyl)oxy)-2-fluoroacetic acid (164a) was chosen as the test substrate for XeF₂-mediated fluorodecarboxylation. Under the fluorodecarboxylation conditions developed by Dr. Claire Chatalova-Sazepin, vigorous bubbling was observed once xenon difluoride was added to the
solution of acid 164a. 19F NMR spectroscopic analysis showed that the yield was only 15% with 64% conversion (Scheme 2.30). We have not yet been able to identify the remainder of the mass balance.

![Scheme 2.30. XeF₂-mediated fluorodecarboxylation of p-bromoaryloxy-fluoroacetic acid (164a).](image)

**Table 2.1.** Condition optimizations on XeF₂-mediated fluorodecarboxylation of acid 164a.

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>XeF₂ (equiv)</th>
<th>t (min)</th>
<th>conc. (M)</th>
<th>Yield (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10</td>
<td>0.5</td>
<td>15</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>30</td>
<td>0.5</td>
<td>17</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>10</td>
<td>0.5</td>
<td>27</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>20</td>
<td>0.5</td>
<td>39</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>20</td>
<td>0.5</td>
<td>48</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>20</td>
<td>0.67</td>
<td>43</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>20</td>
<td>0.33</td>
<td>41</td>
<td>91</td>
</tr>
<tr>
<td>8[b]</td>
<td>3</td>
<td>20</td>
<td>0.5</td>
<td>22</td>
<td>90</td>
</tr>
</tbody>
</table>

[a] Yields were determined by 19F NMR spectroscopy with ethyl trifluoroacetate as internal standard. [b] CD₂Cl₂ was used as the solvent.

We further optimized reaction time and the number of equivalents of xenon difluoride (Table 1). When the reaction time was increased to 30 min, high conversion was achieved but the yield was only slightly increased (Entry 2, Table 1). When two equivalents of xenon difluoride
were added to the reaction, the yield was increased to 27% (Entry 3, Table 1), which was further improved by increasing the reaction time (Entry 4, Table 1). The best yield was obtained when the reaction was conducted with three equivalents of xenon difluoride for 20 min (Entry 5, Table 1). Changing the reaction concentration did not lead to further improvements in the yield (Entry, 6 and 7, Table 1). Due to the poor solubility of the substrate in CDCl₃, CD₂Cl₂ was examined as solvent, but only 22% yield was observed (entry 8).

### 2.4.2 Syntheses of aryl difluoromethyl ethers using XeF₂

To explore the syntheses of aryl difluoromethyl ethers, 2-aryloxy fluoroacetic acids 164a-e were subjected to the optimized conditions. The reactions afforded good yields of the aryl difluoromethyl ether products based on ¹⁹F NMR spectroscopic analysis (Scheme 2.31). In particular, m-bromophenyl difluoromethyl ether (165e) was obtained in excellent yield, which may be attributed to the superior solubility of the corresponding acid substrate.

Reactions were run on 0.2 mmol scale. Yields were presented as the average from more than two repeats within 4% difference, and obtained by ¹⁹F NMR spectroscopy using ethyl trifluoroacetate as the internal standard.

**Scheme 2.31.** Substrate scope investigation for the syntheses of aryl difluoromethyl ethers.
In our studies, the XeF$_2$-mediated fluorodecarboxylation of aryloxy di- and monofluoroacetic acids generally could not account for the full mass balance. We postulated that this could be attributed to the degradation of xenon difluoride or fluoroxenon carboxylate with the formation hydrofluoric acid in the reaction media. To test whether 2-aryloxy difluoroacetate salt could be compatible with the XeF$_2$ reaction and at the same time avoid the formation of hydrofluoric acid, the sodium or tetrabutylammonium salts of 2-(4-(tert-butyl)phenoxy)-2,2-difluoroacetic acid (156a) were subjected to the conditions with XeF$_2$. However, neither carboxylate salts showed reactivity, which could be explained by the necessity of carboxylic acid proton in the $\sigma$-metathesis with XeF$_2$ to form the essential fluoroxenon carboxylate intermediate (Scheme 2.32).

\[
\begin{align*}
R\text{O} & \quad \text{O} \quad \text{O} \\
\text{F} & \quad \text{F} \\
\text{OH} & + \quad \text{XeF}_2 \\
\xrightarrow{\text{$\sigma$-Metathesis}} \\
\text{R}\text{O} & \quad \text{O} \quad \text{Xe} \\
\text{F} & \quad \text{F} \\
\text{HF} & \\
\text{via} \\
\text{R}\text{O} & \quad \text{O} \\
\text{F} & \quad \text{F} \\
\text{H} & \quad \xrightarrow{\text{Fluorodecarboxylation}} \\
\text{F} & \quad \text{Xe} \\
\end{align*}
\]

**Scheme 2.32.** $\sigma$-Metathesis of xenon difluoride with difluoroacetic acid followed by fluorodecarboxylation.

We next investigated different fluoride scavengers, such as silicates and borates, to see whether it can address the issue of mass imbalance and eventually improve the yield of fluoromethyl ether product (Scheme 2.33). The results of the experiments with acid 156a and selected fluoride scavengers showed that tetraethyl silicate and trimethyl borate generally resulted in the decrease on the yield of the desired trifluoromethyl ether. In all of our experiments, a significant amount of starting material remained, which suggests that these fluoride scavengers may preferentially facilitate the degradation of xenon difluoride.\textsuperscript{117}
2.4.3 Exploration of alternative approaches to di- and trifluoromethyl ethers

In the optimization for the XeF$_2$-mediated syntheses of trifluoromethyl ethers, difluoromethyl ether product was observed as a side product, presumably formed through a hydrodecarboxylation process that involves hydrogen atom transfer from solvent CHCl$_3$ to aryloxy difluoromethyl radical intermediate. We hypothesized that the hydrodecarboxylation process could be preferred to the fluorodecarboxylation process if a suitable hydrogen atom donor is present in the reaction. This strategy would allow to access both trifluoromethyl ethers and difluoromethyl ethers from a common starting material: the aryloxy difluoroacetic acid derivative (Scheme 2.34).

To explore the hydrodecarboxylation process, 2-(2,4-dichlorophenyl)oxy)-2,2-difluoroacetic acid (156b) was subjected to the reaction with xenon difluoride with different organic hydrogen atom donors, such as Hantzsch ester, benzaldehyde and isopropanol (Table 2). However, they only afforded poor conversion and yields for both the di- and trifluoromethyl ethers (Table 2).
results suggested that the additives tend to react with xenon difluoride preferentially. Some other hydrogen atom donors were also tested, such as triethylsilane and tris(trimethylsilyl)silane (TTMSS), but gave no yield of the desired products. Instead, vigorous bubbling was observed in the reactions after the addition of the silane reagents, which also indicates the direct reactions between the silanes and xenon difluoride.

To explore alternative radical decarboxylation methods for aryloxy difluoroacetic acids, oxidants, potassium persulfate and bis(trifluoroacetoxy)iodo]benzene (PIFA), were tested on radical decarboxylation of aryloxy-monofluoroacetic acids. However, these oxidants were not able to effect the radical decarboxylation in our experiments, due to the high electrochemical potential of fluoroacetic acids, especially aryl difluoroacetic acids (E° = 2.13 V vs. SHE).¹⁴⁸

| Table 2.2. Selected examples of hydrogen atom donors screening for radical decarboxylation of acid 156b. |
|---|---|---|
| Entry | Additive | Conversion (%) | 165f (%) | 157b (%) |
| 1 | none | 100% | 0% | 41% |
| 2 | benzaldehyde | 46% | 3% | 6% |
| 3 | i-propanol | 12% | 5% | 2% |

Reactions were analyzed by ¹⁹F NMR spectroscopy to determine the conversions and yields.
2.4.4 Exploring XeF$_2$-mediated fluorodecarboxylation for the syntheses of alkyl trifluoromethyl ethers

Due to the superior efficiency of the xenon difluoride-mediated fluorodecarboxylation for the formation of aryl di- and trifluoromethyl ethers, we hypothesized that xenon difluoride might also be able to effect the radical fluorodecarboxylation of alkoxy difluoro acetic acids.

While there are several methods reported for the synthesis of 2-aryloxy difluoroacetic acids, there have not been efficient methods available for syntheses of the analogous 2-alkyloxy difluoroacetic acids. We first tried to prepare a representative 2-alkoxy difluoroacetic acid, 2-$n$-octyloxy difluoroacetic acid (170), by first treating $n$-octanol with sodium hydride followed by adding ethyl bromodifluoroacetate. Unfortunately the desired 2-$($n$$-octyloxy$)$ difluoroacetic acid ethyl ester (169) was not obtained, likely due to a preferential transesterification. After further optimization, it was found that the desired 2-$($n$$-octyloxy$)$ difluoroacetic acid (170) can be directly accessed in 74% yield via the reaction of $n$-octanol with bromodifluoroacetic acid directly using sodium hydride as the base (Scheme 2.35).

$$\text{Scheme 2.35. Synthesis of 2-($n$-octyloxy) difluoroacetic acid 170.}$$

To explore the radical fluorodecarboxylation approach to alkyl trifluoromethyl ethers, acid 170 was subjected to the conditions with one equivalent of xenon difluoride in deuterated chloroform. Good conversion was observed, but the desired trifluoromethyl ether product 171 was detected in poor yield (Scheme 2.36). Increasing the amount of xenon difluoride to two equivalents
led to a further increase in the conversion, but no increase on the yield of the product. $^{19}$F NMR spectroscopic analysis of the crude reaction mixture suggested that several alkyl fluoride-containing products were produced in the reaction. It was hypothesized that xenon difluoride might directly react with the aliphatic chain due to its strong oxidative ability, and the $n$-octyloxy difluoromethyl radical intermediate in the reaction might undergo $\beta$-elimination to form octyl radical, which is more stable and led to octyl fluoride and its derivatives (Scheme 2.37).

Scheme 2.36. Reaction of xenon difluoride with 2-($n$-octyloxy) difluoroacetic acid 170.

Scheme 2.37. Possible processes in the reaction of XeF$_2$ with acid 170.

2.5 Conclusions and outlook

We have successfully applied xenon difluoride-mediated radical fluorodecarboxylation to the syntheses of aryl difluoromethyl ethers from the corresponding 2-aryloxy fluoroacetic acids. This method used mild conditions and demonstrated excellent efficiency, compared to the existing synthetic technologies for the syntheses of aryl di- and trifluoromethyl ethers. However, the xenon difluoride-mediated radical fluorodecarboxylation is not compatible for the syntheses of aliphatic trifluoromethyl ethers, as only low yield was obtained together with alkyl fluoride side-products.
due to the oxidation by xenon difluoride. Overall, we envision that this practical method has the potential in the applications to the syntheses of relevant pharmaceutical or agrochemical molecules that have aryl di- and trifluoromethyl ethers (Figure 2.1).

The investigation on the effects of carboxylate salts and fluoride scavengers indicated that protic acidic conditions were favorable for xenon difluoride-mediated fluorodecarboxylation. Comparing to the literature-reported fluorodecarboxylation by xenon difluoride, the high efficiency of our method for the syntheses of tri- and difluoromethyl ethers could be attributed to larger acidities of the di- and monofluoroacetic acid substrates that accelerate the $\sigma$-metathesis for the formation of xenon ester intermediate.

A divergent approach was investigated for the syntheses of aryl tri- and difluoromethyl ethers from aryloxy difluoroacetic acid via fluoro- and hydrodecarboxylation, respectively. In the investigation on different hydrogen atom donors, xenon difluoride-mediated hydrodecarboxylation of aryloxy difluoroacetic acid was only able to afford very low yields of the difluoromethyl ether due to the direct reactions of hydrogen atom donor reagents with xenon difluoride.

2.6 Experimental information

General methods and instrumentation

All reactions were performed under nitrogen atmosphere unless otherwise noted in the procedures. Anhydrous solvents, such as THF, were obtained by first sparging nitrogen gas through the solvents for one hour and then passing the solvents through activated alumina columns in the Solvent Purification System. Other solvents and reagents were purchased from commercial sources and used as received, unless otherwise stated. Yields refer to chromatographically and
spectroscopically homogeneous materials, unless otherwise noted. The solid phase in the flash chromatography purification was Silicycle F60 silica gel (230-400 mesh).

Infrared spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded using Bruker AV-300 or 400 spectrometers. Low and high-resolution mass spectra were recorded on either a Bruker Esquire-LC spectrometer (LRMS) or a Waters/Micromass LCT spectrometer (for HRMS).

**General procedure A for the syntheses of 2-aryloxy-2-fluoroacetic acids 164**

To a round bottom flask with a stir bar and a solution of the phenol derivative 161 (1 equiv) in anhydrous DMF (0.5 M) under nitrogen atmosphere at room temperature was added K$_2$CO$_3$ (2.5 equiv) and ethyl 2-bromo-2,2-difluoroacetate (162, 1.2 equiv) in one portion. After stirring for overnight, the reaction was diluted with water and extracted with diethyl ether (x 3). The combined organic layers were washed with water (x 2) and brine (x 1), dried over Na$_2$SO$_4$ and concentrated in vacuo to afford crude ester 162, which was used directly in the next step.

The ester 162 was then dissolved in MeOH (0.2 M) at room temperature, and was then added a 4.4 M aqueous solution of NaOH (1.5 equiv) in water. After the reaction proceeded to completion, as monitored by TLC, the solution was concentrated *in vacuo* and diluted with 1.0 M aqueous solution of HCl till pH reached 1 to 2. The mixture was then extracted with ethyl acetate (x 3).
The combined organic layers were washed with brine (x 2), dried over Na$_2$SO$_4$ and concentrated in vacuo to afford pure acid 164.

\[
\begin{align*}
\text{164a} \\
\text{2-(4-bromophenoxy)-2-fluoroacetic acid (164a):} & \quad \text{4-Bromophenol (2.00 g, 11.6 mmol) was subjected to the general procedure A above, 164a was obtained as a white solid (1.66 g) in 63\% yield overall. The characterization data matched the literature data.}^{137} \\
\text{1\textsuperscript{H} NMR} (300 MHz, CDCl$_3$): & \quad \delta 9.69 (s, 1 H), 7.54-7.47 (m, 2 H), 7.08-7.03 (m, 2 H), 5.96 (d, J = 59 Hz, 1 H); \\
\text{19\textsuperscript{F} NMR} (282 MHz, CDCl$_3$): & \quad \delta -130.19 (d, J = 60 Hz, 1 F); \\
\text{13\textsuperscript{C} NMR} (75 MHz, CDCl$_3$): & \quad \delta 168.5 (d, J = 31.3 Hz), 154.6, 133.0, 119.4, 117.7, 102.0 (d, J = 232.5 Hz).
\end{align*}
\]

\[
\begin{align*}
\text{164b} \\
\text{2-(4-chlorophenoxy)-2-fluoroacetic acid (164b):} & \quad \text{4-Chlorophenol (1.00 g, 7.78 mmol) was subjected to the general procedure A above, 164b was obtained as a white solid (1.05 g) in 66\% yield overall. The characterization data matched the literature data.}^{169} \\
\text{1\textsuperscript{H} NMR} (300 MHz, CDCl$_3$): & \quad \delta 10.10 (s, 1 H), 7.40-7.37 (m, 2 H), 7.15-7.12 (m, 2 H), 6.03 (d, J = 60 Hz, 1 H);
\end{align*}
\]
\(^{19}\text{F NMR}\) (282 MHz, CDCl\(_3\)): \(\delta \) -130.12 (d, \(J = 56\) Hz);

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta\) 168.5 (d, \(J = 32.5\) Hz), 154.1, 130.2, 130.0, 119.0, 102.0 (d, \(J = 231.0\) Hz).

\(\text{F} - (4\text{-fluorophenoxy}) - 2\text{-fluoroacetic acid (164d)}\): 4-Fluorophenol (560 mg, 5 mmol) was subjected to the general procedure A above, 164d was obtained as a pale orange solid (832 mg) in 88% yield overall. The characterization data matched the literature data.\(^{137}\)

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\) 7.15-7.10 (m, 2H), 7.08-7.02 (m, 2H), \(\delta\) 5.96 (d, \(J = 59\) Hz, 1H);

\(^{19}\text{F NMR}\) (282 MHz, CDCl\(_3\)): \(\delta\) -117.98, -129.74 (d, \(J = 59.7\) Hz);

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta\) 168.6 (d, \(J = 32.1\) Hz), 159.7 (d, 242.5 Hz), 151.6 (d, 5.75 Hz), 119.5 (d, 10.34 Hz), 116.52 (d, 24.14 Hz), 102.7 (d, \(J = 232.2\) Hz).

\(2\text{-}(3\text{-bromophenoxy}) - 2\text{-fluoroacetic acid (164e)}\): 3-Bromophenol (1.00 g, 5.78 mmol) was subjected to the general procedure A above, 164e was obtained as a pale orange solid (849 mg) in 59% yield overall. The characterization data matched the literature data.\(^{137}\)

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\) 9.33 (s, 1H), 7.35-7.26 (m, 3H), 7.23-7.12 (m, 1H), \(\delta\) 6.03 (d, \(J = 57\) Hz, 1H);
\(^{19}\text{F NMR}\) (282 MHz, CDCl\(_3\)): \(\delta -130.63\) (d, \(J = 56.4\) Hz);

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta 168.2\) (d, \(J = 30.8\) Hz), 156.1, 131.1, 128.0, 123.0, 121.0, 116.2, 101.9 (d, \(J = 231.8\) Hz).

2,2-difluoro-2-(octyloxy)acetic acid (170): To a solution of alcohol 166 (651 mg, 5 mmol) in anhydrous THF (8 mL) was added NaH (600 mg, 15 mmol) as a 60% dispersion in mineral oil in several portions at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 2 h before addition of a solution of bromodifluoroacetic acid (168, 0.78 mL, 6 mmol) in anhydrous THF (7 mL). Then the reaction was stirred at 60 °C for 3 h before quenched with 1.0 M aq. HCl and adjusting pH to be around 1. After further dilution with water (50 mL), the mixture was extracted with EtOAc (80 mL). The organic layer was washed with 0.5 M aq. HCl (50 mL x 2) and brine (100 mL), dried over sodium sulfate and concentrated \textit{in vacuo} to get crude mixture. Purification via silica gel-based flash chromatography (5% to 100% EtOAc in petroleum ethers) to afford acid 170 as a clear liquid (830 mg) in 74% yield (commercially available compound, CAS No. 1153775-41-7).

\(^{1}\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta 5.36\) (br. s, 1 H), 4.04 (t, \(J = 6.6\) Hz, 2 H), 1.74 (quin, \(J = 6.9\) Hz, 2 H), 1.25 - 1.49 (m, 10 H), 0.93 (t, \(J = 6.5\) Hz, 3 H);

\(^{19}\text{F NMR}\) (282 MHz, CDCl\(_3\)): \(\delta -80.0\);

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta 174.5, 114.6, 65.3\) (t, \(J = 5.5\) Hz, 1 C), 31.8, 29.2, 29.1, 29.0, 25.6, 22.7, 14.1.
Chapter 3: Mechanistic Studies on Radical Fluorination

The development of novel synthetic methodologies, such as methods for the synthesis of organofluorine compounds, requires innovation and a deep understanding of chemical reagents and transformations. Driven by the importance of fluorine in pharmaceutical applications, a significant amount of effort has been put into the studies of new fluorinating agents and their reactivities. For instance, the studies on the properties of NFSI and Selectfluor by Sammis and coworkers have led to the discovery of these reagents as versatile atomic fluorine sources. Additionally, based on mechanistic studies on Fe(IV) porphyrin complexes in cytochrome P450 and chloroperoxidase, Groves and coworkers have successfully developed the Mn(IV) porphyrin catalytic system, which is able to apply fluoride salts as atomic fluorine sources in radical fluorinations.

The studies of new atomic fluorine sources and efficient radical fluorination systems have led to the renaissance of radical fluorination as an important technique for the syntheses of organofluorine compounds. This is evidenced by the large number of radical fluorination methodologies developed in the last seven years, using NFSI, Selectfluor and fluoride salts as safe and easy-to-handle atomic fluorine sources. In spite of the novel applications of these reagents, the mechanisms of relevant radical fluorination processes have been underexplored. In particular, there have not been any detailed experimental studies on the mechanism of how the fluorinating agents react with free radicals to form fluorinated products.
In the course of the development of radical fluorination methodologies, the Sammis laboratory became interested in the mechanisms of radical fluorinations with NFSI and Selectfluor.\textsuperscript{136} The goal was to gain useful insights into the reactivity of these reagents, and the mechanisms of the reactions between these reagents and free radicals, which could be important for future development of new synthetic methodologies. This chapter will introduce my work on the mechanistic studies of decarboxylative radical fluorinations using photochemical and silver-catalyzed systems.

3.1 **Mechanisms of radical fluorinations in literature**

A variety of atomic fluorine sources have been used for radical fluorination, starting from the early exploration of hazardous elemental fluorine to currently commercially available, safe and stable reagents, such as NFSI and Selectfluor (Chapter 1, 1.2.3.3). The mechanisms of radical fluorinations are often dependent on the type of fluorinating agents used. The representative mechanisms of radical fluorinations will be introduced below.

3.1.1 **Mechanisms of traditional radical fluorinations**

Radical fluorination by molecular fluorine follows a radical chain mechanism (Scheme 3.1).\textsuperscript{83} The reaction can be initiated through two possible pathways: homolysis of molecular fluorine to form two fluorine radicals, or the reaction of molecular fluorine with a C-H bond to form a fluorine radical and a carbon radical with concomitant formation of one hydrogen fluoride. In the propagation phase, the carbon and fluorine radicals undergo radical transformations to form an alkyl fluoride, while also regenerating a carbon and fluorine radical for further reactions. The termination phase can occur by the coupling of either two carbon radicals or a carbon radical and a fluorine radical to form non-radical molecules.
The radical fluorination step is realized through two pathways: fluorine atom transfer from a molecular fluorine to a carbon radical, or coupling of a carbon radical and a fluorine radical. Due to the weak F-F bond (BDE = 38 kcal/mol), molecular fluorine can undergo homolysis to form two fluorine radicals under thermal or photochemical conditions. The resulting fluorine radicals also react with carbon radicals to form strong C-F bonds (BDE = 90 - 130 kcal/mol). Radical fluorination with molecular fluorine is very exothermic and usually displays poor chemoselectivity. Hypofluorites such as CF₃OF and can react with unsaturated bonds and C-H bonds through a similar radical chain mechanism under photochemical conditions.

Xenon difluoride and high valency metal fluorides, such as AgF₂, CoF₃, MnF₃, and CeF₄, can also be used in radical fluorination methods. For instance, the fluorination of benzene with xenon difluoride was proposed to begin with a SET process between benzene and xenon difluoride to form a benzene radical cation (172), a fluoroxenon radical, and a fluoride ion. The benzene
radical cation can proceed through two possible pathways: (1) formation of a delocalized carbocation $173$ via FAT followed by deprotonation to afford the fluorobenzene, or (2) formation of delocalized carbon radical $174$ via a nucleophilic addition by the fluoride ion, followed by FAT and elimination of hydrogen fluoride to give the fluorobenzene (Scheme 3.2). Although following similar mechanisms in organic reactions, the high valency metal fluorides, AgF$_2$, CoF$_3$, MnF$_3$, and CeF$_4$, normally afford many more products with poor chemoselectivity due to their strong oxidizing abilities.$^{116,219}$

![Scheme 3.2. Two possible pathways in the XeF$_2$-mediated radical fluorination of benzene.](image)

The radical fluorinating step is typically proposed to proceed through a fluorine atom transfer process. However, it has been demonstrated that the xenon difluoride-mediated radical fluorodecarboxylation occurs either through a direct fluorine atom transfer, or through an oxidation of carbon radical to form carbocation before coupling with fluoride.$^{119}$

### 3.1.2 Mechanisms of modern radical fluorinations

In the last seven years, safe and easy-to-handle atomic fluorine sources, such as N-F reagents and fluoride salts, have proved to be versatile reagents for the development of new radical fluorination methodologies. These methodologies have employed a variety of reaction conditions
and mechanisms, including tradition radical generation methods, transition metal catalysis, and photochemical reactions.\textsuperscript{70,72}

The mechanisms of these radical fluorination methodologies vary according to the different methods of radical formation. In the original report of radical fluorinations using N-F reagents by Sammis and coworkers, peresters and diacyl peroxides were used to form alkyl radicals under thermal or photochemical conditions, which then reacted with NFSI or Selectfluor to afford alkyl fluorides (Scheme 1.27). It was proposed that the fluorination step to form alkyl fluorides could occur through two possible pathways: fluorine atom transfer from N-F reagents to alkyl radicals, or SET between the N-F reagents and alkyl radicals to form carbocations before fluoride ion transfer (Figure 3.1).\textsuperscript{136}

\begin{align*}
&\text{Fluorine Atom Transfer} \\
&\text{SET} \\
&R^\bullet + \text{Y-F} \rightarrow ? \rightarrow R=F + \text{Y}^\bullet \\
&\text{Y-F = N-F reagents, M-F species.}
\end{align*}

\textbf{Figure 3.1.} The possible pathways for radical fluorination by different fluorinating species.

In the first report of transition metal-catalyzed radical fluorination of aliphatic carboxylic acids, Li and coworkers, proposed a silver catalytic cycle that involves the formation of a Ag(III)-F species (176), based on the precedent of Ag(III) mediated decarboxylation of mandelate ion.\textsuperscript{220} It was proposed by Li and coworkers that a Ag(III) species effects the oxidative radical decarboxylation of a carboxylic acid to form an alkyl radical and a Ag(II)-F species (177). These two intermediates react to regenerate Ag(I) and afford the alkyl fluoride product (Scheme 3.3).\textsuperscript{139}
In 2012, Lectka and coworkers reported a poly-component copper-catalyzed aliphatic C-H radical fluorination (Scheme 1.28, 4). Subsequent mechanistic studies suggested that this reaction operates in a radical chain mechanism, which begins with the reaction between a Cu(I) species and Selectfluor to form a radical dication species $178$. $178$ is the key intermediate to propagate the radical chain by hydrogen atom abstraction from a C-H bond to form $179$ and an alkyl radical that further reacts with another Selectfluor molecule to regenerate $178$ (Scheme 3.4).$^{142}$

Scheme 3.3. Proposed mechanism of silver-catalyzed radical fluorodecarboxylation of aliphatic acids.

Scheme 3.4. Proposed radical chain mechanism of copper-catalyzed C-H bond radical fluorination.
Several different radical fluorination mechanisms have been proposed in other fluorination methodologies. Groves and coworkers proposed that manganese porphyrin-catalyzed C-H radical fluorination involves a fluorine atom rebound from the manganese catalyst to the alkyl radicals.\textsuperscript{143} Li and coworkers, in their recent report of a carbofluorination of alkenes, proposed a copper fluoride dimer $[\text{Cu}_2\text{F}_2\text{L}_2]^{2+}$ to be the active species to react with alkyl radicals to form the C-F bonds.\textsuperscript{221}

3.1.3 Knowledge gaps in the mechanisms of radical fluorinations

While many mechanisms have been hypothesized for radical fluorinations with N-F reagents, there have not been any reported experimental studies on the exact mechanism of fluorination of alkyl radicals. In the original report from the Sammis laboratory, N-F reagents and transition metal fluorides have been proposed to be the active species to react with free radicals to afford the fluorinated products. The fluorination mechanism is often postulated as direct fluorine atom transfer process. However, N-F reagents can also be used as oxidants in redox reactions, and are proposed to undergo SET in electrophilic fluorinations.\textsuperscript{126-128} Additionally, the early studies by Kochi on organic redox reactions by metal complexes suggested that organic free radicals can react with transition metal complexes in either a SET or a ligand transfer process, which is dependent on transition metals and their coordination environments.\textsuperscript{222,223}

In collaboration with Dr. Chaozhong Li’s laboratory, we embarked on our investigation into the mechanisms of radical fluorinations using photochemical and silver-catalyzed radical decarboxylation systems. The goal of our studies is to gain a better understanding of the reactivities of different fluorinating species, such as N-F reagents, toward free radicals. While our mechanistic studies were underway, Flowers and Patel investigated the mechanism of silver-catalyzed
decarboxylative radical fluorination method, although they did not offer explanations on the mechanisms of the radical fluorination step.\textsuperscript{224}

### 3.2 Experimental designs

Two possible pathways for radical fluorinations, direct fluorine atom transfer and SET followed by fluoride trapping (Figure 3.2), both start with the formation of carbon radicals. The main difference between the two is that the second pathway proceeds through a carbocation intermediate. All of our experiments in this section focus on methods to indirectly test for the presence of a carbocation, through either carbocation rearrangement or nucleophilic trapping of the cation.

#### 3.2.1 Experimental designs for carbocation rearrangement

The first set of experiments focused on utilizing a semi-pinacol rearrangement to test for the presence of a cation intermediate. As a test substrate, we prepared $\beta$-hydroxy carboxylic acid \textbf{180}, along with the corresponding perester \textbf{181}. These two substrates can be converted to carboxyl radical \textbf{182} under transition metal-catalyzed redox processes, photochemical, or thermal conditions. The carboxyl radical \textbf{182} can further undergo radical decarboxylation to form the primary alkyl radical \textbf{183} (Scheme 3.5), which can react further through several possible pathways (Scheme 3.6). It can be converted to an alkyl fluoride \textbf{184} through fluorine atom transfer (FAT) (Scheme 3.6, pathway 1), or be converted to carbocation \textbf{185} if SET occurs with radical \textbf{183}. Then \textbf{185} could couple with a fluoride ion to form \textbf{184}, or undergo semi-pinacol rearrangement to form a more stable oxonium species before deprotonation to form a ketone \textbf{187} (Scheme 3.6, pathway 2). While it is also possible that radical \textbf{183} could proceed through a rearrangement leading to ketone \textbf{187} (Scheme 3.6, pathway 3), literature reports indicated that the rate of 1,2-radical phenyl
rearrangement has a rate constant around $10^2$ (for neophyl radical 1,2-rearrangement: $k = 402$ s$^{-1}$ at 298 K). Hence, the formation of rearranged products can be an indication of the carbocation intermediate 185 in the radical fluorination that corresponds to the SET/fluorination pathways (Figure 3.2).

![Scheme 3.5. Mechanism of forming primary alkyl radical from β-hydroxy carboxylic acid or perester.](image)

Scheme 3.5. Mechanism of forming primary alkyl radical from β-hydroxy carboxylic acid or perester.

![Scheme 3.6. Possible paths for carbon radical 183.](image)

Scheme 3.6. Possible paths for carbon radical 183.

3.2.2 Experimental designs for trapping carbocation with nucleophiles

One of the distinctive features of carbocations compared to carbon radicals is their ability to react with various heteroatom-based nucleophiles, such as oxygenated nucleophiles and amines. To distinguish the pathways of radical fluorinations, we surmised that potential carbocation
intermediates may be trapped by suitable nucleophiles if the carbocations have sufficiently long lifetimes.

2-Phenylacetic acid (188) and its derivatives were utilized as the substrates for our carbocation trapping experiments (Figure 3.2). Carboxylic acids 188, 189, and 190 can be converted to primary, secondary and tertiary benzyl radicals, respectively, via oxidative radical decarboxylation. If these radicals undergo SET under radical fluorination conditions, the resultant benzyl cations might have sufficiently long lifetimes, due to resonance stabilization, to be trapped by solvents or nucleophiles. The change from primary, secondary to tertiary benzyl radicals results in a progressive decrease in their electrochemical potentials, as well as an increase in the lifetimes of the corresponding carbocations, which may offer additional insight into possible SET processes (Figure 3.3).

Figure 3.2. Substrate designs for trapping carbocations and the relevant paths in radical fluorination.
Figure 3.3. Trends in the electrochemical potentials of benzyl radicals and the stability of benzyl cations.

3.3 Results and discussions

3.3.1 Mechanistic studies on the radical fluorinations by N-F reagents

All of our mechanistic studies focused on the decarboxylative radical fluorination methods that were previously developed in the Sammis laboratory, as well as the silver-catalyzed decarboxylative radical fluorination methodology developed by Prof. Chaozhong Li’s laboratory.

3.3.1.1 Mechanistic studies with carbocation rearrangement strategy

β-Hydroxy carboxylic acid 180 was synthesized through an aldol reaction between acetophenone and a dianionic enolate, formed in situ by double deprotonations of acetic acid. The perester 181 was prepared from the acid using a DCC-mediated coupling reaction (Scheme 3.7).

Scheme 3.7. Synthesis of carboxylic acid 180 and perester 181.
As previously discussed in Section 3.21, radical 183 may undergo a radical rearrangement pathway to generate 187 (Scheme 3.6, pathway 3). To determine whether this rearrangement pathway is possible to occur, a control experiment was conducted by subjecting perester 181 to the photochemical conditions in the absence of a N-F reagent. *t*ert-Butyl ether 191 was the only product and no ketone product 187 was detected based on $^1$H NMR spectroscopic analysis (Scheme 3.8). This confirms that radical rearrangement pathway is significantly slower than coupling with *t*ert-butoxy radical to form the ether 191.

![Scheme 3.8. Control experiment of perester 181 using UV irradiation.](image)

To investigate the photochemical radical fluorination, perester 181 was subjected to photochemical conditions with NFSI or Selectfluor as the radical fluorinating agent. Analysis of $^1$H NMR spectroscopic data indicated that ketone 187, resulting from rearrangement, was not present in either of the two reactions. The reaction with Selectfluor afforded both the alkyl fluoride 184 and *t*ert-buty1 ether 191 in a 1:10 ratio, while the reaction with NFSI only gave trace alkyl fluoride 184, with the major product being the ether 191 (Scheme 3.9). These results are consistent with the fluorine atom transfer mechanism. The difference between the ratios of alkyl fluoride 184 to the ether 191 is also consistent with the computational results that NFSI has a stronger N-F bond than Selectfluor.\textsuperscript{136}
3.3.1.2 Mechanistic studies with cation trapping strategy

We next explored the carbocation trapping strategy using benzylic acid derivatives 188, 189, and 190 (Figure 3.3). If a carbocation is formed from any of these substrates, it may be trapped by water to form the corresponding alcohol. 2-Phenyl acetic acid (188) was subjected to the photo-decarboxylative radical fluorination conditions with water as the solvent (Scheme 3.10). The NMR spectroscopic analysis of the reaction mixture showed that only the expected benzyl fluoride was obtained. Similarly, a photo-decarboxylative radical fluorination of 2-phenylpropionic acid (189) only afforded corresponding benzyl fluoride (Scheme 3.10). However, the decarboxylative radical fluorination of 2-methyl-2-phenylpropionic acid (190) gave a mixture of benzyl fluoride 194 and alcohol 197 in 2:1 ratio. As a control reaction, the benzyl fluoride product was subjected to the reaction conditions, and none of the corresponding alcohol was observed. These results suggest that the alcohol 197 is generated from the tertiary carbocation formed from corresponding benzyl radical through a SET process. Furthermore, primary and secondary benzyl radicals either were not oxidized, or the carbocation intermediates do not have long enough lifetimes to be trapped by
water. The different experimental outcome of the tertiary benzyl radical is consistent with its low redox potential, compared to the primary and secondary radicals.

Scheme 3.10. Photodecarboxylative radical fluorination of benzyl carboxylic acids.

To corroborate the hypothesis that SET is not able to occur between Selectfluor and a primary benzyl radical, potassium benzyl trifluoroborate (198) was subjected to a Ir photoredox catalytic radical fluorination with Selectfluor in aqueous solvents under visible light (Scheme 3.11), an unpublished method developed by my colleague Dr. Claire Chatalova-Sazepin. In this method, the benzyl trifluoroborate salt 198 can be converted to a benzyl radical via oxidation by an Ir(IV) catalytic species, before further reaction with Selectfluor to form a benzyl fluoride (192). NMR spectroscopic analysis of the reaction mixture indicated that only benzyl fluoride (192) was formed with no alcohol 195 observed. In all, these results are more consistent with the mechanism in which Selectfluor reacts with primary alkyl radicals via fluorine atom transfer, instead of SET/fluoride transfer pathway.
3.3.2 **Mechanistic studies on the radical fluorination in a silver catalytic system**

We next investigated the mechanism of the silver-catalyzed radical fluorination method. Our mechanistic studies on the silver-catalyzed decarboxylative radical fluorination was in collaboration with Dr. Chaozhong Li’s group. The goals are to probe the possible carbocation intermediates, and also the role of Selectfluor in the silver-catalyzed fluorination processes. While this project was a collaborative effort, only the experimental results that I performed will be presented in the subsequent sections.

3.3.2.1 **Mechanistic studies using carbocation rearrangement strategy**

We began our investigations into the silver-catalyzed fluorination mechanism using β-hydroxy carboxylic acid 180 (Scheme 3.12). NMR spectroscopic analysis of the reaction mixture showed the formation of alkyl fluoride 184 as expected, together with two ketone products, 2-fluoro-2-phenyl acetone (199) and 2-phenyl acetone (187), in the ratio of 2 : 1 : 1, which was determined by the proton integrations of methylene of 184, methine of 199, and methylene of
187 in the 1H NMR spectrum of the reaction mixture. A control experiment indicated that the fluoroketone product 199 was produced from 187 under the silver catalytic conditions, confirming that both 187 and 199 are products of the semi-pinacol rearrangement. As radical rearrangement does not occur at an appreciable rate compared to fluorine atom transfer (Scheme 3.6), these results suggested that a primary carbocation is formed under these reaction conditions.


To investigate the role of Selectfluor in the silver-catalyzed reaction conditions, different loadings of Selectfluor were examined in the decarboxylative radical fluorination of acid 180. As the amount of Selectfluor was increased, the product ratio increasingly favored the alkyl fluoride 184 over the ketone products, 199 and 187, (Table 3.1). When ten equivalents of Selectfluor was used, the alkyl fluoride 184 was almost the only product in the reaction (Table 3.1, Entry 4). This result is consistent with our experiments in Sections 3.3.1.1 and 3.3.1.2, which demonstrated that Selectfluor is likely to react with alkyl radicals via fluorine atom transfer. The increase of the product ratios of alkyl fluoride to ketones can be attributed to the increase of Selectfluor concentration in the silver-catalyzed fluorination reactions. These results suggest that Selectfluor is involved in the direct fluorination of the alkyl radicals via fluorine atom transfer. However, our results do not either support or contradict Prof. Li’s hypothesis that a Ag-F species is also involved in the fluorination reaction.
Table 3.1. Different loading of Selectfluor in silver-catalyzed decarboxylative radical fluorination.

<table>
<thead>
<tr>
<th>Entry</th>
<th>x equiv (Selectfluor)</th>
<th>Ratios (184 : 199 + 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.33 : 1</td>
</tr>
<tr>
<td>2</td>
<td>0.8</td>
<td>0.5 : 1</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>1 : 1</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>17 : 1</td>
</tr>
</tbody>
</table>

Ratios were determined by $^1$H NMR and $^{19}$F NMR spectroscopic analyses of the reaction mixtures.

We next performed a similar study as the experiment with a large amount of Selectfluor, but with an excess of NFSI added to the reaction (Scheme 3.13). The addition of eight equivalents to the standard reaction conditions led to an increase in the amount of alkyl fluoride 184 relative to the ketone products (Scheme 3.13). The increase was not as large as that with ten equivalents of Selectfluor (Table 3.1, Entry 1), which is consistent with the computational results that NFSI is not as good an atomic fluorine source as Selectfluor.$^{136}$

Scheme 3.13. Ag-catalyzed radical fluorination of 180 with Selectfluor and NFSI.

In all, the results above demonstrated that, in the silver-catalyzed decarboxylative radical fluorination of acids, Selectfluor reacts directly with alkyl radicals via fluorine atom transfer to form alkyl fluorides (Figure 3.4). However, it does not exclude the possibility that a catalytic silver
species (Ag\textsuperscript{n+}F) reacts with alkyl radicals to form alkyl fluorides through fluorine atom transfer or the SET/fluoride abstraction sequence.

![Diagram](image)

**Figure 3.4.** Selectfluor- and silver-mediated fluorination of alkyl radicals after radical decarboxylation.

We next examined the effects of solvent and concentration on the product distribution. We hypothesized that solvents may affect the fluorine atom transfer, an intermolecular process, more than the monomolecular semi-pinacol rearrangement. The solvent system of the silver-catalyzed fluorination of 180 was first replaced with only water, which resulted in an increase of the product ratio in favor of the alkyl fluoride (Table 3.2, entry 2). We inferred that the result could be due to the emulsion or solvent cage formed between Selectfluor and the organic substrate in water, considering that Selectfluor consists of two organic ion pairs. The microenvironment of solvent cage could facilitate the intermolecular fluorine atom transfer process between Selectfluor and the alkyl radical, which resulted in the increase of the alkyl fluoride in the product ratio. A similar increase of the product ratio in favor of the alkyl fluoride was also observed when the concentration of the reaction was doubled (Table 3.2, Entry 3). This may be due to an increased rate of the bimolecular fluorine atom transfer process, compared to the carbocation rearrangement.
**Table 3.2.** The effects of solvent and concentration in the silver-catalyzed decarboxylative radical fluorination.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Concentration (M)</th>
<th>Ratios (180 : 199 + 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O/acetone (1 : 1)</td>
<td>0.06</td>
<td>1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>0.06</td>
<td>2.2 : 1</td>
</tr>
<tr>
<td>3</td>
<td>H₂O/acetone (1 : 1)</td>
<td>0.12</td>
<td>2.4 : 1</td>
</tr>
</tbody>
</table>

Ratios were determined by ¹H NMR and ¹⁹F NMR spectroscopic analyses of the reaction mixtures.

Different silver catalyst loadings were then investigated. Higher concentrations of the high-oxidation state silver species may facilitate the formation of carbocation, and therefore the formation of ketones. The results showed that increased catalyst loadings led to only a slight increase in the product ratio in favor of the rearranged products (Table 3.3). However, due to the low solubility of silver carboxylate, these experiments do not suggest a clear effect of the catalyst on the fluorination processes.

**Table 3.3.** The effect of the loading of silver catalyst in the silver-catalyzed decarboxylative radical fluorination.

<table>
<thead>
<tr>
<th>Entry</th>
<th>x</th>
<th>Ratios (180 : 199 + 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>0.9 : 1</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>0.9 : 1</td>
</tr>
</tbody>
</table>

Ratios were determined by ¹H NMR and ¹⁹F NMR spectroscopic analyses of the reaction mixtures.
3.3.2.2 Mechanistic studies using cation trapping strategy

2-Phenyl carboxylic acids were used as substrates in mechanistic studies examining the silver-catalyzed fluorodecarboxylation. Acids 188, 189, and 190 were subjected to the standard silver catalytic conditions (Scheme 3.15). In contrast to the results from the photochemical fluorodecarboxylation reactions (Scheme 3.10), these reactions all generated alcohol or alcohol-derived products, such as benzaldehyde or acetophenone (Scheme 3.14). Control experiments showed that benzyl fluoride (192) is stable under the reaction conditions, and is only converted to the corresponding alcohol in 10% conversion under reflux after 12 hours. Furthermore, control reactions indicated that benzyl alcohol 195 can be readily converted to the benzaldehyde under the same reaction conditions. The ratios between cation-trapped products and benzyl fluorides increase with the increasing substitution of the radical intermediate. This is consistent with the trend of electrochemical potentials of primary, secondary and tertiary benzyl radicals. In all, the results suggested that oxidations occurred with the primary, secondary and tertiary benzyl radical intermediates in the reactions to form the corresponding carbocations, which were trapped by water to afford the alcohols. Having already demonstrated that Selectfluor is not able to oxidize primary and secondary benzyl radicals (Scheme 3.11), we surmised that the oxidation of the primary and secondary benzyl radicals is likely effected by a Ag$^{n+}$ catalytic species (Scheme 3.15).

Scheme 3.15. Illustration on the formation of carbocations and derivatives.

To confirm the formation of carbocations, different nucleophiles, such as chloride, ethoxide, cyanide, acetate, and benzene, were tested to trap the carbocations in the reaction of 2-phenyl acetic acid (188), (Table 3.4). Chloride and cyanide completely inhibited the reactions (Table 3.4, Entry 2 and 3). Benzene was also tested as it may react with a carbocation, but is less prone to participate in redox processes in the silver-catalyzed reactions. However, no benzene-trapped product was observed.
Table 3.4. Experiments of different nucleophiles to trap the benzyl cation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Ratios (188 : 192 : 195 : 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>0 : 1 : 2.6</td>
</tr>
<tr>
<td>2</td>
<td>3 equiv KCl</td>
<td>no conversion</td>
</tr>
<tr>
<td>3</td>
<td>3 equiv KCN</td>
<td>no conversion</td>
</tr>
<tr>
<td>4</td>
<td>3 equiv NaOEt</td>
<td>1 : 1.8 : 0.3 : 0</td>
</tr>
<tr>
<td>5</td>
<td>6 equiv benzene</td>
<td>0 : 2.5 : 1 : 0</td>
</tr>
<tr>
<td>6</td>
<td>1 mL benzene</td>
<td>0 : 2.5 : 1 : 0</td>
</tr>
</tbody>
</table>

Ratios were determined by $^1$H NMR spectroscopic analyses of the reaction mixtures.

Scheme 3.16. Ag-catalyzed decarboxylative radical fluorination of benzyl acid 188 with NaOAc and the control experiment.

Acetate was then examined as a nucleophile to trap the carbocation in the reaction of 188. Several products resulting from nucleophilic addition to the carbocation were observed, including benzyl alcohol (195), benzyl acetate (201), benzyl 2-phenylacetate (202), and benzaldehyde (Scheme 3.16, A). In a control experiment, subjecting the benzyl fluoride to the same conditions with sodium acetate did not afford benzyl acetate, and only very a small amount of benzyl alcohol
was formed (Scheme 3.16, B). This result excludes the possibility of forming benzyl acetate through nucleophilic substitution of benzyl fluoride.

We hypothesized that the formation of both benzyl acetate (201) and benzyl 2-phenylacetate (202) may be attributed to the presence of both acetate and 2-phenyl acetate anions in the reaction, since they have comparable basicity. Therefore, sodium benzoate, a weaker base than general aliphatic carboxylates, was utilized as the nucleophile to trap the carbocation (Scheme 3.17). We observed only benzyl alcohol and benzyl benzoate as carbocation trapping products.

Scheme 3.17. Nucleophile-trapping experiment with NaOBz in Ag-catalyzed radical fluorodecarboxylation of 188.

Our mechanistic studies using a carbocation trapping strategy support the pathway of silver-mediated oxidation of carbon radicals to carbocations, which can be trapped by nucleophiles in situ to afford corresponding products, such as alcohols and esters. The observation of carbocation intermediates is consistent with the semi-pinacol rearrangement we observed with β-hydroxyl carboxylic acid 180 in the carbocation rearrangement experiments (Scheme 3.12).

3.4 Conclusions

The mechanisms of radical fluorinations using photochemical and thermal reactions, or silver-catalyzed radical decarboxylation, were studied to gain a better understanding of the reactivities of different N-F fluorinating reagents toward free radicals. The investigation focused on two different modes of fluorine transfer: direct fluorine transfer, and a SET step followed by
fluoride trapping. These two mechanistic pathways were probed using substrates that could either undergo a carbocation rearrangement, or substrates that were susceptible to carbocation trapping.

Initial studies focused on photofluorodecarboxylations of acids and peresters using Selectfluor or NFSI. Overall, the results from our mechanistic studies are more consistent with a direct fluorine transfer from either Selectfluor or NFSI to alkyl radicals. The only evidence for a SET pathway was observed with a substrate that is prone to oxidation, a tertiary benzyl radical.

Studies then focused on the silver-catalyzed fluorodecarboxylation conditions. Carboxylic acids, such as $\beta$-hydroxyl carboxylic acid and benzylic acids, were used in the mechanistic studies of silver-catalyzed radical fluorination with Selectfluor. Our results suggest that Selectfluor is directly involved in the radical fluorination of alkyl radicals to form alkyl fluorides through a fluorine-atom transfer pathway. In all cases, products resulting from a SET process were observed, which suggests that oxidation of the alkyl radicals is due to the silver species and not the N-F reagent. Further studies will explore whether the carbocation formed via SET with silver species is a key intermediate that might lead to the formation of alkyl fluorides.

3.5 Experimental information

General methods and instrumentation

All reactions were performed under nitrogen atmosphere unless otherwise noted in the procedures. Anhydrous solvents such as THF were obtained by first sparging nitrogen gas through the solvents for one hour and then passing the solvents through activated alumina columns in the Solvent Purification System. Other solvents and reagents were purchased from commercial sources and used as received, unless otherwise stated. Yields refer to chromatographically and
spectroscopically homogeneous materials, unless otherwise noted. The solid phase in the flash chromatography purification was Silicycle F60 silica gel (230-400 mesh).

Infrared spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded using a Bruker AV-300 or 400 spectrometers. Low and high-resolution mass spectra were recorded on either a Bruker Esquire-LC spectrometer (LRMS) or a Waters/Micromass LCT spectrometer (for HRMS).

**Syntheses of intermediates and starting materials.**

![Chemical structure](image)

**3-hydroxy-3-phenylbutanoic acid (180):** To a round bottom flask equipped with a stir bar and a solution of diisopropylamine (5.75 mL, 42 mmol) in anhydrous THF (60 mL) at −78 °C was added a 1.35 M solution of n-butyl lithium in hexanes (37 mL, 50 mmol) over 10 min. After stirring for 5 min, the mixture turned light yellow and to this was added glacial acetic acid (1.14 mL, 20 mmol) dropwise. Then the reaction mixture was stirred for 30 min at 0 °C, during which the color turned from light yellow to pale white. The reaction mixture was then added a solution of acetophenone (7 mL, 60 mmol) in 30 mL anhydrous THF at −78 °C in 10 min. The reaction was allowed to warm up over about 2 h before quenched with 0.1 M NaOH aqueous solution (~5 mL). The mixture was then extracted with 0.1 M NaOH aqueous solution (50 mL x 3). The combined aqueous layers were acidified with 4 M HCl aqueous solution till the pH reached 1~2 before exaction with ethyl acetate (60 mL x 3). The combined organic layer was dried over sodium sulfate and concentrated *in vacuo* to obtain the crude mixture which was purified via silica gel-
based flash chromatography (2% to 33% EtOAc in petroleum ethers) to afford acid 180 (2.82 g) in 78% yield as a pale white solid.

**IR (neat):** 3509, 3089, 3061, 3029, 2982, 2935, 2873, 1753, 1447, 1389, 1367, 1321, 1186, 1156, 1119, 765, 699 cm⁻¹;

**¹H NMR** (300 MHz, CDCl₃): δ 7.40 - 7.47 (m, 2 H), 7.30 - 7.39 (m, 2 H), 7.22 - 7.30 (m, 1 H), 3.03 (d, J = 16.4 Hz, 1 H), 2.84 (d, J = 16.4 Hz, 1 H), 1.56 (s, 3 H);

**¹³C NMR** (75 MHz, CDCl₃): δ 177.4, 146.3, 128.5, 127.2, 124.4, 72.9, 46.1, 30.6;

**HRMS-ESI(m/z):** calcd. for C₁₀H₁₄NaO₃ [M+Na]⁺ 203.0682, found 203.0684.

**tert-butyl 3-hydroxy-3-phenylbutaneperoxoate (181):** To a solution of acid 180 (540 mg, 3 mmol) in dichloromethane (DCM, 30 mL) was added 4-(dimethylamino)pyridine (37 mg, 0.3 mmol) and a 5.5 M solution of tert-butyl hydrogen peroxide in decane (0.6 mL, 3.3 mmol). The mixture was then cooled to 0 °C and stirred for 5 min before the addition of a solution of DCC (619 mg, 3.3 mmol) in DCM (16 mL). The reaction was further stirred for 30 min at 0 °C before warmed up to room temperature and stirred overnight. The reaction mixture was then filtered through celite and concentrated *in vacuo* to obtain crude mixture which was purified via silica gel-based flash chromatography (5% to 10% EtOAc in petroleum ethers) to afford perester 181 (785 mg) in 94% yield as a clear colorless liquid.

**IR (neat):** 3509, 3089, 3061, 3029, 2982, 2935, 2873, 1753, 1447, 1389, 1367, 1321, 1186, 1156, 1119, 765, 699 cm⁻¹;
**H NMR** (300 MHz, CDCl$_3$): $\delta$ 7.40 - 7.47 (m, 2 H), 7.27 - 7.35 (m, 2 H), 7.17 - 7.24 (m, 1 H), 4.13 (s, 1 H), 2.92 (d, $J = 15.4$ Hz, 1 H), 2.75 (d, $J = 15.4$ Hz, 1 H), 1.57 (s, 3 H), 1.14 (s, 9 H);

**C NMR** (75 MHz, CDCl$_3$): $\delta$ 170.1, 146.4, 128.5, 127.3, 124.7, 83.9, 73.1, 43.9, 30.6, 26.0;

**HRMS-ESI($m/z$)**: calcd. for C$_{14}$H$_{20}$NaO$_4$ [M+Na]$^+$ 275.1259, found 275.1262.

**methyl 2-phenylpropanoate (204):** To a solution of diisopropylamine (3.4 mL, 24 mmol) in anhydrous THF (30 mL) at $-78 \, ^\circ C$ under nitrogen atmosphere was added a 1.54 M solution of n-butyllithium in hexanes (15.6 mL) slowly. The mixture was stirred for 10 min at $-78 \, ^\circ C$ before the addition of a solution of methyl 2-phenylacetate (2.8 mL, 20 mmol) in anhydrous THF at 0 $\, ^\circ C$ in 50 min. Finally, methyl iodide (3.74 mL, 60 mmol) was added in one portion at $-78 \, ^\circ C$ and the reaction was then allowed to warm up to room temperature and stirred overnight. After quenched with aqueous saturated solution of NH$_4$Cl (30 mL), the mixture was diluted with water (20 mL) and extracted with diethyl ether (20 mL x 3). The combined organic layers were washed with brine (60 mL), dried over sodium sulfate and concentrated *in vacuo* to give the crude mixture which was further purified via silica gel-based flash chromatography (2% to 10% EtOAc in petroleum ethers) to afford methylated ester 204 as a liquid (3.13g) in 95% yield. The characterization data matched the literature data.$^{227}$

**H NMR** (300 MHz, CDCl$_3$): $\delta$ 7.57 (dd, $J = 7.8$, 1.1 Hz, 1 H), 7.37 - 7.29 (m, 1 H), 7.24 - 7.11 (m, 2 H), 4.70 (s, 2 H), 4.09 (br. s, 2 H), 1.49 (s, 9 H);

**C NMR** (75 MHz, CDCl$_3$): $\delta$ 156.9, 137.0, 132.9, 128.6, 128.5, 127.4, 123.1, 81.1, 54.6, 28.4.
methyl 2-methyl-2-phenylpropanoate (205): Following the procedure for the synthesis of ester 204, ester 205 was obtained as a liquid (1.43 g) in 89% yield. The characterization data matched the literature data.228

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.34 - 7.42 (m, 4 H), 7.26 - 7.34 (m, 1 H), 3.71 (s, 3 H), 1.64 (s, 6 H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 177.3, 144.7, 128.3, 126.7, 125.6, 52.2, 46.6, 26.6.

2-phenylacetic acid (188): To a solution of methyl 2-phenylacetate (2.84 mL, 20 mmol) in methanol (40 mL) at room temperature was added a 2.5 M aqueous solution of sodium hydroxide (10 mL, 25 mmol). The mixture was then stirred at reflux temperature for 16 h. After cooling to room temperature, the mixture was concentrated in vacuo and then washed with diethyl ether (10 mL). The remaining aqueous layer was then acidified with a 4 M solution of HCl (26 mL) and extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate and concentrated in vacuo to afford the final product 188 as a white solid (2.58 g) in 95% yield. The characterization data matched the literature data.229

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.10 (br. s, 1 H), 7.42 - 7.29 (m, 5 H), 3.70 (s, 2 H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 178.2, 133.5, 129.6, 128.9, 127.6, 41.3.
2-phenylpropanoic acid (189): Following the procedure for the synthesis of acid 188, the acid 189 was afforded as a clear colorless liquid in quantitative yield. The characterization data matched the literature data.229

$^1$H NMR (300 MHz, CDCl$_3$): \( \delta \) 11.09 (br. s, 1 H), 7.32 - 7.53 (m, 5 H), 3.84 (q, \( J = 7.1 \) Hz, 1 H), 1.62 (d, \( J = 7.3 \) Hz, 3 H);

$^{13}$C NMR (75 MHz, CDCl$_3$): \( \delta \) 181.2, 139.8, 128.8, 127.7, 127.5, 45.5, 18.2.

2-methyl-2-phenylpropanoic acid (190): Following the procedure for the synthesis of acid 188, the acid 190 was afforded as a clear colorless liquid in quantitative yield. The characterization data matched the literature data.230

$^1$H NMR (300 MHz, CDCl$_3$): \( \delta \) 12.16 (br. s, 1 H), 7.48 - 7.31 (m, 5 H), 1.66 (s, 6 H);

$^{13}$C NMR (75 MHz, CDCl$_3$): \( \delta \) 183.8, 144.0, 128.6, 127.2, 126.0, 46.5, 26.4.
Chapter 4: Regiocontrolled and Stereoselective Syntheses of Tetrahydrophthalazines via Radical Cyclization

Nitrogen heterocycles are prevalent in natural products and bioactive molecules (for representative examples, see Figure 4.1). In particular, nitrogen heterocycles play pivotal roles in pharmaceuticals. Statistical data show that approximately 59% of U.S. FDA approved...
small-molecule drugs contain at least one nitrogen heterocycle, and 231 (66%) of all the 351 ring systems contained in small-molecule drugs are nitrogen heterocycles.\textsuperscript{17,231} The importance of nitrogen heterocycles in pharmaceuticals can be attributed to their rich structural diversity, with respect to ring size, ring type and substitution pattern. This diversity provides a wide range of physiochemical properties for drug discovery.

The importance of nitrogen heterocycles has led to substantial efforts towards the development of new and efficient synthetic methodologies for their preparations. Such methods include the applications of transition metal or organo-catalytic reactions,\textsuperscript{234-236} pericyclic reactions, and a large number of condensation reactions.\textsuperscript{232}

In spite of the numerous advancements, there are still many pharmaceutically interesting nitrogen heterocycles that are challenging to access efficiently and selectively using existing synthetic technologies. Two examples of the challenging nitrogen heterocycles are di- and tetrahydrophthalazines (Figure 4.2), which have found important utilities in pharmaceutically relevant molecules.\textsuperscript{237-242} The symmetry of the structures and the partially saturated ring with a N-N bond, impose significant challenges in their syntheses, especially for 1,4-substituted tetrahydrophthalazines.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.2.png}
\caption{Di- and tetrahydrophthalazines, 212 and 213.}
\end{figure}

In the course of the development of new radical methodologies, the Sammis laboratory conceived a new approach using a key radical cyclization that can effectively address the relevant
This chapter will start with general introductions on phthalazines and their applications, and radical cyclizations, and then detail the work I performed on the development of a new method for the syntheses of phthalazine derivatives.

4.1 Importance of di- and tetrahydrophthalazines

Phthalazine derivatives, such as aromatic phthalazines, phthalazinones, di- and tetrahydrophthalazines, have found important applications in pharmaceuticals. For instance, In 1970, Sandoz Wander Inc. discovered a series of drug analogs featuring tetrahydrophthalazine ring systems that are central nervous system (CNS) stimulants (214, Figure 4.3). These compounds contain fused tricyclic structures with substituents at 1 position of the tetrahydrophthalazine. Shortly after, they discovered a similar class of analogs with a tetrahydrophthalazine ring system, which are bioactive as central nervous system depressants.

In 1987, USV Pharmaceutical Corporate discovered a series of tetrahydrophthalazine-based drug analogs that have antihypertension activity. All these analogs contain substituents at 1, 2, and 3 positions (215, Figure 4.3).

![Molecules](image)

**Figure 4.3.** Examples of pharmaceutically active molecules with di- or tetrahydrophthalazines.

Dihydrophthalazine-based drug analogs have been shown to be allosteric AMPA receptor modulators or non-NMDA inotropic excitatory amino acid receptor antagonists. These
analogs contain substituents at the 1, 2, and 4 positions of the dihydrophthalazine ring, and also on the benzene rings (216, Figure 4.3).

4.2 Synthetic methods for phthalazine derivatives in literature

4.2.1 Traditional approaches

The most commonly used strategy for the syntheses of substituted phthalazine derivatives starts with the preparation of high oxidation-state phthalazines, such as 1,4-phthalazinedione or phthalazine. These intermediates are then derivatized, through either aromatic addition or reduction processes, to access di- and tetrahydrophthalazines (Figure 4.4).

![Figure 4.4. Common strategies for the syntheses of phthalazine derivatives.](image)

The starting molecules such as 1,4-phthalazinediones or phthalazines used in this strategy have symmetric and planar ring structures, which significantly impede the control of regio- and stereochemistry in the functionalizations of 1 or 4 positions. For instance, in the syntheses of antitumor phthalazine analogs 221 and 222, a 1,4,6-trichlorophthalazine intermediate was first prepared from the corresponding 1,4-phthalazinedione 217 (Scheme 4.1). However, the nucleophilic aromatic substitution of the 1,4,6-trichlorophthalazine with a piperazine 218 afforded no regioselectivity between 1 and 4 positions, and a 1:1 mixture of 6- and 7-chlorophthalazines (219 and 220) was formed. The subsequent functionalization of the other C-Cl bond was completed through a Negishi cross coupling reaction.
Phthalazine rings can also be synthesized from benzo diketones, which in turn can be accessed from the corresponding mono-ketones through an ortho-metalation/acylation sequence (Figure 4.5). This route generally displays poor regioselectivity in the ortho-metalation/acylation step. The regioselectivity issue is reflected in the lack of diversity of the substituents on the benzene ring in the relevant drug analogs.\textsuperscript{239,240} For instance, the synthesis of 216 began with the formation of 1,2-dicarbonyl benzene 225 through ortho-lithiation of 4-methoxybenzaldehyde (223), and subsequent acylation with a Weinreb amide 224. This approach intrinsically has regioselectivity issue when the meta-substituted aryl aldehydes are used (Scheme 4.2).

\textbf{Scheme 4.1.} Syntheses of 1,4-disubstituted phthalazine analogs from phthalazinedione.

\textbf{Figure 4.5.} Synthesis of phthalazine from 1,4-diketone.
The conversion of aromatic phthalazines to di- or tetrahydrophthalazines usually makes use of the intrinsic electron-deficiency of the 1 and 4 positions. Thus, most of the methods used for these transformations are nucleophilic addition or reduction. For example, in the synthesis of 216, phthalazine 226 was converted to the 4-methyl dihydrophthalazine 227 through a nucleophilic addition of methyl lithium to the 4 position of 226. The regiochemistry was set by blocking 1-position with an aryl substituent, but there was no stereochemical control in the addition. In another example of nucleophilic additions to phthalazine (228), poor chemoselectivity was demonstrated and a mixture of di- and tetrahydrophthalazines was formed (Scheme 4.3). Ruxer et al. explored using pre-activation through the formation of N-alkyl phthalazinium intermediate 231 in order to control the chemoselectivity (Scheme 4.4). However, this process still did not result in any stereochemical control.
Scheme 4.3. Nucleophilic addition of perfluorohexyllithium to phthalazine.

Scheme 4.4. Employment of N-alkyl phthalazinium in the reduction or nucleophilic addition of phthalazine.\textsuperscript{247}

Tetrahydrophthalazine-based drug analogs 239, were reported to possess activity as central nerve system depressants.\textsuperscript{237} The syntheses of these analogs generally started with the preparation of phthalazinones 238 from \textit{ortho}-(arylcarbonyl) benzoic acids 237, followed by lithium aluminum hydride (LAH) reduction to access racemic pyrazolo tetrahydrophthalazines 239 (Scheme 4.5).
4.2.2 Challenges in the synthesis of di- and tetrahydrophthalazines

The existing synthetic technologies for di- and tetrahydrophthalazines as introduced above, present two significant problems: (1) it is challenging to control regioselectivity in the syntheses of starting phthalazines; (2) there has been no case of stereochemical control in the conversion of high-oxidation state phthalazines to di- and tetrahydrophthalazines. In particular, there have been no example of regio- and stereoselective routes to 1,4-disubstituted tetrahydrophthalazines.

4.2.3 Cyclization approaches to access tetrahydrophthalazine derivatives

An alternative approach to tetrahydrophthalazine derivatives would be a cyclization reaction to form the partially saturated nitrogen heterocycle from pre-functionalized starting materials with the appropriate regio- or stereochemistry. Theoretically, this cyclization can be achieved through the formation of either a C-C bond or a C-N bond to form the diazene ring (Figure 4.6). There have been a few cyclization methods reported in literature that can directly access substituted di- or tetrahydrophthalazines which will be discussed in detail in the following section.

**Figure 4.6.** Retrosynthetic analysis of the cyclization methods for tetrahydrophthalazines.
4.2.3.1 Ionic cyclization

Two electron processes (ionic) have demonstrated prominent versatility in the traditional synthetic methodologies of nitrogen heterocycles. In respect to tetrahydrophthalazines, the earliest report of a cyclization method, by Kametani et al., made use of a Pictet-Spengler-type reaction (Scheme 4.6).\textsuperscript{249} This method requires the use of a hydrazone substrate tethered to an electron-rich aryl ring with electron-donating groups at meta position so that nucleophilic aromatic substitution (SNAr) could be realized to form tetrahydrophthalazine products. This reaction uses harsh conditions with hydrochloric acid and high temperature, which result in significant limitations on the functional group tolerance and substitution pattern of the phthalazine products.

Scheme 4.6. Syntheses of tetrahydrophthalazines via Pictet-Spengler-type reaction.

Recently, Li and coworkers creatively employed azomethine ylides of arylaldehydes \textsuperscript{242} as starting materials in a rhodium-catalyzed oxidative C-H functionalization/cyclization sequence to directly access 1,2-dihydropthalazine products.\textsuperscript{250} The regioselectivity of rhodium-catalyzed C-H activation can be influenced by the sterics of the ligands on rhodium. However, side products were usually formed due to further C-H functionalization of the products. By adjusting the equivalents of reagents and the choices of solvents, the desired products can be favored (Scheme 4.7, 1). Shortly after, Li’s laboratory further developed a silver-catalyzed nucleophilic addition/6-exo-trig cyclization tandem reaction to synthesize 1,4-disubstituted hydrophthalazine derivatives from ortho-alkynyl aryl azomethine ylides \textsuperscript{245} (Scheme 4.7, 2).\textsuperscript{251} This method is limited to the
syntheses of these tricyclic structures and is unable to control the stereochemistry. Additionally, further steps are required to synthesize 1,4-disubstituted tetrahydrophthalazines.

**Scheme 4.7.** Transition metal-catalyzed syntheses of hydrophthalazine derivatives via ionic cyclization of azomethine ylides.

### 4.2.3.2 Radical cyclizations to afford tetrahydrophthalazines

We hypothesized that radical cyclizations could be a viable approach to construct the tetrahydrophthalazine rings. Radical cyclizations are often able to tolerate substrates with diverse electronic properties, as neutral free radicals are the active species in the reaction.\(^8\)

**Scheme 4.8.** *6-Endo-trig* radical cyclization to convert hydrazone to substituted tetrahydrophthalazine.
4.3 Radical cyclization onto C=N bonds

To the best of our knowledge, the 6-endo-trig radical cyclization onto hydrazones, not only
is an unprecedented synthetic approach to tetrahydrophthalazines, but also represents an
underexplored reactivity pattern of 6-endo radical cyclization onto C=N based motifs, such as
imines, oximes, and hydrazones.\(^{252}\) To provide a thorough evaluation, the development of radical
cyclization onto C=N bonds will be briefly introduced in this section.

4.3.1 General features of radical cyclizations onto C=N bonds

C=N bonds have been used as electrophiles in ionic reactions (i.e. Mannich reaction) for
more than a century.\(^{253}\) The introduction of C=N bonds as radical acceptors in radical reactions
was not explored until the 1980s. According to kinetic studies, carbon radicals generally react
several magnitudes faster with C=N bonds than C=C bonds.\(^ {252}\)

\[
\begin{align*}
&\text{Nucleophilic addition} \\
&\text{Radical addition}
\end{align*}
\]

\[
\begin{align*}
\text{N}^+ & \quad \text{R}^1 \quad \text{R}^2 \\
\text{R}^3 & \quad \text{N} \quad \text{R}^1 \quad \text{R}^2
\end{align*}
\]

\[
\begin{align*}
\text{Nu}^- & \quad \text{R}^1 \quad \text{R}^2 \\
\text{N} & \quad \text{R}^1 \quad \text{R}^2
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{N}^- \quad \text{R}^1 \\
\text{R} & \quad \text{N} \quad \text{R}^1 \\
\end{align*}
\]

Scheme 4.9. Nucleophilic addition and radical addition onto C=N bonds.

Imines, oximes and hydrazones are the most common C=N bonds radical acceptors in radical
additions or radical cyclizations. For imines, oximes and hydrazones, computational and
experimental results have demonstrated that radicals typically add to the carbons of the C=N
bonds, due to their larger LUMO coefficients, instead of nitrogens.\(^ {254-256}\) However, radical
additions or cyclizations have been shown to occur on the nitrogens in several cases. Bowman\( et \ al.\) reported that the 5-exo-trig radical cyclizations of imines \(^{247}\) and \(^{250}\) were preferred to the 6-
endo radical cyclization, and the regioselectivity was enhanced when 5-exo cyclizations coincide with radical attack at the carbons of the C=N bonds (Scheme 4.10, 1 and 2). These results indicated that the stereoelectronic factors are more influential than the LUMO coefficients of C=N bonds in radical cyclizations onto imines. Steric effects can also influence the chemoselectivity, as seen in the 5-exo cyclization of ketimine 253 (Scheme 4.10, 3).

Scheme 4.10. 5-Exo/6-endo competition in radical cyclization onto imines.

Radical cyclizations of aryl radicals onto aldimines prefers the 6-endo radical cyclization to the 5-exo, as shown by the 12 : 1 product ratio of 257 and 258 (Scheme 4.11). Kinetic studies have revealed that the 6-endo cyclization has slightly larger rate constant than the 5-exo pathway, although the products from both pathways are usually formed (Scheme 4.11). This preference of cyclization onto the carbon atom was also seen during the synthesis of racemic cryptostyline analog 260 (Scheme 4.12, 1). The regioselectivity would be reversed to favor the 5-exo radical cyclization pathway when ketimines, such as 262, were used as substrates (Scheme 4.12, 2).
Imines, oximes and hydrazones have been extensively studied in exo radical cyclizations, and they generally demonstrate different chemical behaviors (Scheme 4.13). Specifically, oximes and hydrazones showed excellent regioselectivity in radical cyclization; only products resulting from radical cyclizations at carbons of C=N bonds were obtained. This selectivity can be attributed to the large LUMO coefficients at the carbons, as well as the good stability of the nitrogen-centered radicals resulted from the adjacent heteroatoms. In addition, kinetic data have shown that radical cyclizations onto oximes and hydrazones generally have larger rate constants than analogous cyclizations onto imines (Figure 4.7).
Scheme 4.13. Exo radical cyclization onto C=N bonds of imines, oximes and hydrazones.

Figure 4.7. Exo radical cyclization onto C=N bonds of imines, oximes and hydrazones, and relevant rate constants

4.3.2 Types of radical cyclizations onto C=N bonds

A variety of methods utilizing different functional groups and initiation systems have been developed for radical cyclizations onto imines, oximes and hydrazones. These methods can be generally categorized into three types: reductive, redox-neutral and oxidative radical cyclizations.

Reductive radical cyclizations generally utilize reagents, such as SmI$_2$, Bu$_3$SnH, silanes, and reducing metals. This type of radical cyclization normally uses carbon-centered radical precursors, such as carbonyl, thionocarbonates, organohalides, organoselenides, alkenes, alkynes or allenes. The first radical cyclization onto C=N bonds, reported by Corey et al. in 1983, used a Zn/TMSCl system to generate ketyl radicals from oxime-tethered cyclopentanones for a 5-exo-trig radical cyclization onto the oximes (Scheme 4.14). The cis-stereoselectivity of this radical cyclization can be explained by the Beckwith-Houk model, in which the cyclization proceeds through a chair-like transition state. The oxime C=N bond is in a pseudo-equatorial position to avoid 1,2-strain from the cyclopentane ring, as well as 1,3-strain from the pseudo-axial hydrogen.
atom of the methylenyl group. Chelation of zinc ion with the oxime may also contribute to the stereoselectivity.

\[
\begin{align*}
\text{Favored TS:} & \\
\end{align*}
\]

**Scheme 4.14.** Reductive 5-\textit{exo}-\textit{trig} radical cyclization onto C=N of oxime using a Zn/TMSCl system.

Redox-neutral radical cyclizations onto C=N bonds generally involve the incorporation of the radical chain carriers into the cyclized products, or utilize redox-neutral catalytic systems. The substrates used for this type of radical cyclizations generally possess alkenes, alkynes and allenes that can be converted to carbon-centered radicals via intermolecular radical additions. Reagents, such as organosilanes and tin hydrides, and thiols, react with the substrates to form the desired radical, resulting in thiyl, silyl or organotin functionalized products. For example, Naito and coworkers in the investigations of radical cyclizations of alkene-tethered oximes and hydrazones, \(^{267}\), utilized 5-\textit{exo}-\textit{trig} radical cyclizations initiated by thiy radical additions to alkenes (Scheme 4.15).\(^{265}\) Their studies indicated that \textit{cis}-diastereomers were slightly favored in all cases, and oximes substrates generally gave better diastereoselectivity than hydrazones. In another example, Zhu and coworkers reported a photoredox catalytic cascade radical cyclization of \textit{ortho}-alkynyl aryl hydrazones \(^{269}\), including a 6-\textit{exo} radical cyclization (Scheme 4.16). This cascade process begins with the formation of a malonyl radical from a malonyl bromide \(^{270}\) via SET form a photoexcited
Ir catalyst, followed by a radical addition to the alkyne group and subsequent cascade radical cyclization.$^{266}$

\[ \begin{align*}
X = \text{CH}_2, \text{C(CO}_2\text{Et)}_2, \text{NTs}, \text{O} \\
R = \text{OMe}, \text{OBn}, \text{NPh}_2
\end{align*} \]

**Scheme 4.15.** Alkene-tethered oximes and hydrazones for radical cyclizations initiated via intermolecular radical addition by a thiol radical.

\[ \begin{align*}
\text{267} & \quad \text{PhSH, AIBN, Benzene, reflux} \\
\text{268} & \quad 49-88\% \\
& \quad \text{cis/trans} = 1.2 : 1 \text{ to } 4.0 : 1
\end{align*} \]

Oxidative radical cyclization onto C=N bonds normally utilize a stoichiometric or excess amount of oxidants to effect the transformations. For instance, Bode and coworkers reported the oxidative radical cyclizations onto imines for the syntheses of saturated nitrogen heterocycles, such as morpholines, thiomorpholines, and piperazines, from aldehydes through a one-pot process (Scheme 4.16).$^{267-269}$ The one-pot process involves the formation of imines **273** from aldehydes and aminotributylstannanes **272**, followed by the treatment with a stoichiometric amount of copper oxidant to enable the 6-*endo-trig* radical cyclization. This protocol demonstrated good to excellent diastereoselectivities ($>20 : 1$) for amine substrates with $R^1$ substituent at the $\alpha$-position. Shortly after, Bode and coworkers further developed a redox-neutral copper catalytic system without using a stoichiometric amount of the copper oxidant in radical cyclizations onto imines.$^{269}$
In addition, they recently have applied organosilane-tethered amines as reagents to perform similar radical cyclizations using redox-neutral iridium photoredox catalytic systems.²⁷⁰,²⁷¹

\[
\begin{align*}
\text{R}^1, \text{R}^2 &= \text{Ar, alkyl} \\
M &= \text{SnBu}_3, \text{SiMe}_3
\end{align*}
\]

**Scheme 4.17.** Organostannane- or silane-tethered amines for the syntheses of saturated nitrogen heterocycles via Cu or Ir photoredox catalysis.

### 4.3.3 **Endo mode of radical cyclization onto C=N bonds**

*Exo* radical cyclizations onto C=N bonds have been much more extensively explored than *endo*. In particular, oximes and hydrazones have been the most commonly used substrates in various methodologies featuring *exo* radical cyclizations. In contrast, *endo* radical cyclizations have been demonstrated with imines by Bode and coworkers, in the oxidative or redox-neutral *endo* radical cyclizations onto imines. Bode and coworkers also reported reductive 6-*endo-trig* radical cyclization of imines for the syntheses of tetrahydronaphthyridines from heterocyclic aryl bromide-tethered imines.²⁷²

In spite of the advancement of *endo* radical cyclization onto imines, there have been no reports of *endo* radical cyclization onto oximes, and only a few examples on hydrazones. For example, the attempted 6-*endo* radical cyclization of hydrazone 275, reported by Bowman and coworkers in 1995, was unsuccessful, and only the dehalogenated product 276 was observed (Scheme 4.18).²⁵⁷
Scheme 4.18. The first attempt of 6-endo-trig radical cyclization of a hydrazone by Bowman and coworkers.

The Sammis group reported the first example of endo radical cyclization onto hydrazones in 2014. This reaction utilized tosyl-hydrazone as the radical acceptors for the reductive 6-endo-trig radical cyclization in the syntheses of 1,3-dienes directly from aldehydes through a sequential and cascade protocol (Scheme 4.19). The tosyl-hydrazone 279 are formed through condensation reactions between aldehydes and tosylhydrazides, such as 278, followed by the radical cyclization/pericyclic cascade reactions in one-pot under the reflux conditions with Bu3SnH and AIBN. The radical/pericyclic cascade starts with the formation of vinyl radical 280 through radical substitutions of 279 with a tributyltin radical, and then the 6-endo-trig radical cyclizations onto C=N bonds of 280 afford the key N-tetrahydropyrazidine radicals 281, which undergoes β-elimination and cycloreversion to afford 1,3-dienes 282 through diazene intermediates.

Scheme 4.19. 6-Endo-trig radical cyclization of hydrazone as the key step for the conversion of aldehyde to diene in a sequential/cascade protocol.
Another example of an *endo* radical cyclization onto hydrazones was reported by Bode and coworkers in 2017, based on their previous copper-mediated oxidative radical cyclizations onto imines. In this new method, they successfully applied a hydrazinetributylstannane reagent for the syntheses of 7-membered cyclic hydrazones through an oxidative *7-endo-trig* radical cyclization of hydrazones using a stoichiometric amount of copper (II) triflate as the oxidant (Scheme 4.20).

![Scheme 4.20](image)

**Scheme 4.20.** Oxidative *7-endo-trig* radical cyclization of a hydrazone prepared from a hydrazinetributylstannane.

In all, *endo* radical cyclization onto C=N bonds of oximes and hydrazones are underdeveloped compared to imines. The challenges of *endo* radical cyclizations of oximes and hydrazones may be attributed to the increased rigidity of the large conjugation systems in oximes and hydrazones, which could make it difficult to adjust molecular conformations for the cyclization processes.

### 4.4 Results and discussions

We began our studies into *6-endo-trig* radical cyclizations onto hydrazones, in order to explore new approaches for the syntheses of tetrahydrophthalazines. In particular, our goal was to develop a robust and efficient method using radical cyclization that could address the challenges of controlling regio- and stereoselectivities in the syntheses of multi-substituted tetrahydrophthalazine, especially 1,4-disubstituted tetrahydrophthalazines.
4.4.1 Optimizations of the 6-endo-trig radical cyclization of hydrazones

The one-pot sequential/cascade protocol previously developed in the Sammis laboratory for the syntheses of 1,3-dienes was only successful with aliphatic aldehydes (Scheme 4.19), and cannot tolerate certain motifs, including aryl, benzyl and glyoxylate hydrazones, and ester functional groups. However, these motifs, especially aryl groups, are important and common in phthalazine-based drug analogs (Figure 4.3). To ensure our new method would work for aryl hydrazones, we selected an aryl Boc-hydrazone as the substrate for the optimizations of the 6-endo-trig radical cyclizations of hydrazones. Boc was chosen instead of tosyl as the protecting group to prevent the nitrogen-centered tetrahydrophthalazine radical from $\beta$-elimination, which would lead to dihydrophthalazines (Scheme 4.21).

![Scheme 4.21. Possible structural scrambling through $\beta$-elimination of the protecting group.](image)

Optimization experiments began with the treatment of Boc-hydrazone 286 with the original conditions used in the 1,3-diene synthesis; to the solution of 286 in anhydrous toluene under reflux and inert atmosphere was slowly added the solution of Bu$_3$SnH and AIBN in anhydrous toluene over 4 hours (Table 4.1, Entry 1). In contrast to what was previously observed, the reaction obtained a 20% conversion to the desired tetrahydrophthalazine 287 based on $^1$H NMR spectroscopic analysis of the crude reaction mixture.
With this promising result, we next examined triethylborane/O\textsubscript{2} system. This initiation method was selected as it can be used to initiate radical processes at low temperatures, which is often advantageous to achieve better stereoselectivity\textsuperscript{,274} compared to the other thermal initiation systems. The first trial was conducted by using a slow addition of Bu\textsubscript{3}SnH solution slowly to the solution of hydrazone 286 and an excess of triethylborane over 4 hours at –78 °C under anhydrous conditions in a nitrogen atmosphere (Table 4.1, Entry 2). After stirring for 6 h overall, we observed a 28% conversion of 286 to the cyclized Boc-protected tetrahydrophthalazine 287, which demonstrated the compatibility of triethylborane/O\textsubscript{2} system with this radical cyclization. It was hypothesized that the low conversion may be due to the degradation of triethylborane during the slow addition of Bu\textsubscript{3}SnH. To test this hypothesis, this reaction was then conducted with all reagents added in one portion (Table 4.1, Entry 3). This reaction achieved full conversion and, more importantly, only the desired tetrahydrophthalazine 287 was generated and no cyclization at the nitrogen atom of C=N bond was observed. Although a slow addition of Bu\textsubscript{3}SnH is generally required for the competition against the formation of dehalogenated product via HAT in radical cyclizations of organohalides, no products from dehalogenation were observed in this radical cyclization, which indicates a fast \textit{endo} radical cyclization rate onto hydrazone and is drastically different from literature examples of \textit{6-endo-trig} radical cyclization onto imines. We further tested the reaction with only one equivalent of triethylborane, but almost no conversion was obtained (Table 4.1, Entry 4).
Table 4.1. Optimization of the radical cyclization of hydrazone 286 under inert atmosphere.

![Chemical structure of hydrazone 286 and reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>x [H]</th>
<th>y (Et$_3$B)</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conversion (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^a$</td>
<td>2.5 equiv Bu$_3$SnH</td>
<td>0.2 equiv AIBN</td>
<td>reflux</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>(instead of Et$_3$B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2$^b$</td>
<td>1.5 equiv Bu$_3$SnH</td>
<td>10</td>
<td>-78→rt</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>1.5 equiv Bu$_3$SnH</td>
<td>10</td>
<td>-78→rt</td>
<td>6</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>1.5 equiv Bu$_3$SnH</td>
<td>1.0</td>
<td>-78→rt</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>3.0 equiv (TMS)$_3$SiH</td>
<td>10</td>
<td>-78→rt</td>
<td>52</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>3.0 equiv (TMS)$_3$SiH</td>
<td>10</td>
<td>50</td>
<td>6</td>
<td>&gt;95</td>
</tr>
<tr>
<td>7</td>
<td>1.5 equiv (TMS)$_3$SiH</td>
<td>10</td>
<td>50</td>
<td>6</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

All optimization reactions were run on 0.10 mmol scale under N$_2$ atmosphere with anhydrous toluene as the solvent, unless otherwise noted, and Et$_3$B was a reagent purchased as a 1.0 M solution in hexanes in inert atmosphere. $^a$[H] reagent and AIBN were added slowly as a solution in anhydrous toluene over 4 h. $^b$[H] reagent was added slowly as a 0.2 M solution in anhydrous toluene over 4 h. $^c$Conversions to 287 were determined via $^1$H NMR spectroscopy of the crude reaction mixture.

We next explored the use of tris(trimethylsilyl)silane (TTMSS) as the hydride source in the reaction, which is a less toxic reagent than tributyltin hydride (acute oral LD$_{50}$ = 94–234 mg/kg for rat) (Table 4.1, Entry 5). The reaction required longer time to reach high conversion, which is probably due to the larger BDE(Si–H) of TTMSS than BDE(Sn–H) of Bu$_3$SnH (Table 1.1). The reaction was able to afford 91% conversion to the cyclized product with no obvious side-products detected by $^1$H NMR spectroscopy. Further exploration showed that the sluggish reaction
time can be addressed by using an elevated reaction temperature (Table 1.1, Entry 6). In addition, the amount of TTMSS can be reduced to one and a half equivalents without compromising the conversion (Table 1.1, Entry 7).

To test the robustness of this method, we investigated whether this hydrazone radical cyclization is able to tolerate air and moisture. The reaction of 286 was conducted under air atmosphere in toluene that was not specially dried (Table 4.2, Entry 1). The reaction proceeded to 84% conversion with only a small amount of remaining starting material. The conversion was next improved by using three equivalents of TTMSS (Table 4.2, Entry 2). After further optimization on the amount of reagents, we found that two and a half equivalents of TTMSS and five equivalents of triethylborane are sufficient to afford full conversion to the desired product (Table 4.2, Entry 3 to 7). Optimization on the reaction temperature and time also revealed that the reaction can be run at room temperature in 1.5 hours to afford full conversion to the product (Table 4.2, Entry 8). When the reaction was scaled up to 1.0 mmol scale, an 87% isolated yield of the desired Boc-protected tetrahydrophthalazine 287 was obtained.
Table 4.2. Optimization of the radical cyclization of hydrazone 286 with \((\text{TMS})_3\text{SiH}\) under air.

![Optimization Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>(x) ((\text{TMS})_3\text{SiH})</th>
<th>(y) ((\text{Et}_3\text{B}))</th>
<th>(T) (^\circ\text{C})</th>
<th>(t) (\text{h})</th>
<th>Conversion (%)(^{[a]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>10</td>
<td>50</td>
<td>6</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>10</td>
<td>50</td>
<td>6</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>10</td>
<td>50</td>
<td>6</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>10</td>
<td>50</td>
<td>6</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>5</td>
<td>50</td>
<td>6</td>
<td>&gt;95</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>2.5</td>
<td>50</td>
<td>6</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>1.0</td>
<td>50</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
<td>5</td>
<td>rt</td>
<td>1.5</td>
<td>&gt;95 (87)(^{[b]})</td>
</tr>
</tbody>
</table>

All optimization reactions were run on 0.10 mmol scale under air atmosphere with toluene as the solvent that was not specially dried. \(\text{Et}_3\text{B}\) was a reagent purchased as a 1.0 M solution in hexanes in inert atmosphere. \(^{[a]}\) Conversions to 287 were determined via \(^1\text{H}\) NMR spectroscopy of the crude reaction mixture. \(^{[b]}\) Isolated yield on 1.5 mmol scale.

4.4.2 One-pot or stepwise protocols

With the optimized conditions for the 6-endo-trig radical cyclization of hydrazones in hand, we next explored whether it is possible to directly access the substituted tetrahydrophthalazines from aldehydes, Boc-hydrazone, and aryl bromides. We explored two synthetic routes to the tetrahydrophthalazines: (1) Benzylation/condensation/radical cyclization; (2) condensation/benzylation/radical cyclization (Scheme 4.22).
Scheme 4.22. Synthetic protocols to access tetrahydrophthalazines.

The route 1 starts with an \( S_N2 \) reaction between \( o \)-bromobenzyl bromide and Boc-hydrazide to form the benzylicated Boc-hydrazide, followed by the condensation reaction with an aldehyde to afford the hydrazone 288 for radical cyclization (Scheme 4.22). In this route, we hypothesized that a one-pot process may combine the condensation reaction with the radical cyclization to increase the synthetic efficiency. To test this one-pot process, benzaldehyde and hydrazide 289 were stirred in 1:1 mol ratio in toluene with sodium sulfate as the desiccant. After full conversion was reached, to the reaction mixture was further added TTMSS and triethylborane to initiate the radical cyclization. However, after testing the reactions with different amount of reagents, we found that this one-pot process required ten equivalents of triethylborane to achieve good conversion, and only afforded the tetrahydrophthalazine 287 in 76% isolated yield, slightly lower than the step-wise process (87%).
After further condition investigation, the following one-pot process was established as a general protocol for converting an aldehyde and hydrazide 289 to a tetrahydrophthalazine: An aldehyde and hydrazide 289 efficiently undergo condensation to form hydrazone in ethanol (0.5 M) at room temperature. After full conversion, the mixture was concentrated in vacuo, and then was directly dissolved in toluene (0.02 M) and two and a half equivalents of TTMSS and five equivalents of triethylborane were added for the radical cyclization under air atmosphere. The reaction was concentrated in vacuo after designated reaction time, and was subjected to silica gel-based flash chromatography purification to afford the tetrahydrophthalazine product. Using this protocol, an 85% isolated yield of the tetrahydrophthalazine 287 was obtained, comparable to the step-wise fashion. This protocol also does not require the use of desiccant and extra triethylborane.

Route 2 starts with the condensation between the Boc-hydrazide and an aldehyde to form a hydrazone, which was further used in the nucleophilic substitution reaction ortho-bromobenzyl bromide to afford hydrazone 288. For the synthestic process with benzaldehyde, we found that the nucleophilic substitution was able to afford the benzylated hydrazone 286 in quantitative yield after aqueous work-up, which doesn’t require further purification before being used for radical cyclization to form tetrahydrophthalazine 287.
4.4.3 **Substrate scope study for the syntheses of tetrahydrophthalazines**

With the established protocols for the syntheses of tetrahydrophthalazines, we next explored the substrate scope. The one-pot reaction protocol outlined in route 1 demonstrated excellent substrate tolerance and were able to afford substituted tetrahydrophthalazines 287, 290-308 in high yields (Scheme 4.24). Specifically, substrates with electron withdrawing or electron donating groups on the arenes, and heterocycles, such as pyridine and furan, gave the cyclized products 290-300 in 57-96% yields. In addition, aliphatic aldehydes were tolerated in the reactions to form 1-alkyl tetrahydrophthalazines 301-307 in 42-95% yields, regardless of the steric hindrance of the alkyl groups. 1-Alkoxycarbonyl tetrahydrophthalazine 308 was efficiently synthesized from glyoxylate and 289 in 89% yield. Furthermore, a hydrazone with an aryl iodine instead of aryl bromide was also able to afford the corresponding tetrahydrophthalazine 301 in a good yield. Interestingly, vinyl or styryl-tethered hydrazones only afforded the desired tetrahydrophthalazines without undergoing further 5-exo-trig radical cyclizations onto olefins to form tricyclic products. These results suggested that triethylborane could be coordinating with the hydrazones, which may prohibit a subsequent radical cyclization of the nitrogen-centered radical intermediates. MS and NMR spectroscopic analysis of crude reaction mixture of the vinyl-tethered hydrazone indicated that a hydrosilylation side product was formed along with 306 under the reaction conditions.
Scheme 4.24. Syntheses of tetrahydrophthalazines with 1-substitution from aldehydes and hydrazide 288.

We next explored the syntheses of unsymmetrical tetrahydrophthalazines. The regiochemistry of substituents R₁ and R₂ on phthalazines are normally challenging to control in
the syntheses of drug analogs (Chapter 4, Section 4.2). To demonstrate that our synthetic protocols could control the regiochemistry of the tetrahydrophthalazine products, we explored the cyclization of hydrazones with different substituents on benzene ring, such as fluorine, methoxyl and morpholine. Following our standard conditions of radical cyclizations, the three multi-substituted tetrahydrophthalazines 309-311 were synthesized in excellent yields (Scheme 4.25).

![Scheme 4.25. Syntheses of tetrahydrophthalazines with substitutions on the benzene ring.](image)

**4.4.4 Diastereoselectivity studies**

We further explored the diastereoselective syntheses of 1,4-disubstituted tetrahydrophthalazines, which was conducted in collaboration with my colleague Jia Yi Mo in the Sammis laboratory. To investigate the feasibility of the diastereoselective radical cyclizations, hydrazone 312 with a methyl substituent on the benzyl position was prepared by Jia Yi Mo through route 2 (Scheme 4.22). Then I performed a radical cyclization of 312 under the standard conditions, but the analysis by $^1$H NMR spectroscopy revealed that the desired cyclic product was formed together with a significant amount of dehalogenated product 314. This result indicated the competition between HAT and the $\delta$-endo-trig radical cyclization. However, the NMR
spectroscopic analysis of cyclized product 313 showed that the radical cyclization afforded an excellent diastereoselectivity and only the trans-diastereomer was produced.

![Scheme 4.26. Radical cyclization of 312 under the standard radical cyclization conditions.](image)

To optimize the chemoselectivity for the favor of 6-endo-trig radical cyclization, Jia Yi Mo and I further investigated the effect of temperature, as we hypothesized that they could be influential in the competition between intra- and intermolecular reactions of the aryl radical intermediate. Thus, the reaction of hydrazone 312 was conducted at 80 °C and we observed slight increase of the product ratio of 313 and 314 from 1.2 : 1 to 1.8 : 1. My colleague Jia Yi Mo also examined different temperatures, as well as different addition rates of TTMSS to the reaction mixture, in order to decrease the rate of HAT process by keeping the hydride reagent at low concentration during the reaction. However, the product ratio was not improved, and remained around 2 : 1. We proposed that the congested structural environment of the hydrazone 312 may result in a significant energy barrier for the rotation of the benzyl C-N bond of the corresponding aryl radical intermediate, which makes the conformational rearrangement unfavorable for radical cyclization, but is beneficial for intermolecular HAT with TTMSS (Scheme 4.27).
We hypothesized that the nonpolar solvent, toluene, may not be favorable for the conformational rearrangement of the relative polar hydrazones. Thus, different polar solvents were tested to facilitate the rotation of the C-N bond. Additionally, polar solvents may have a “cage effect” on the nonpolar TTMSS molecules, which could hinder the intermolecular HAT process so that the product ratio could be improved. Therefore, my colleague, Jia Yi Mo examined solvents such as DCM and ethanol, and I examined acetonitrile and methanol. Our results showed that polar solvents are able to increase the product ratio, but significant increases were only observed when protic solvents, such as ethanol and methanol were used. The reaction with methanol was able to produce the desired tetrahydrophthalazine 313 as the only product in 80% isolated yield with excellent diastereoselectivity. Phenyl substituted hydrazone 315 was also investigated, and was able to afford the trans-tetrahydrophthalazine product 316 in good yield (Scheme 4.28).

Scheme 4.27. Illustration on the rotation of benzyl C-N bond of hydrazone 312.

Scheme 4.28. Syntheses of 1,4-disubstituted tetrahydrophthalazines with excellent chemo- and diastereoselectivity.
4.4.5 Mechanistic studies

4.4.5.1 Mechanistic proposals for the 6-endo-trig radical cyclization

The mechanism of radical reactions initiated by Et₃B/O₂ and hydride reagents have been extensively studied, and is generally accepted to be a radical chain process. We proposed that the 6-endo-trig radical cyclization of hydrazones in our method also follows a radical chain mechanism. In this respect, taking the reaction of hydrazone 286 as an example, the initiation phase starts with the reaction of a Et₃B with a molecular oxygen to form an ethyl radical, followed by HAT with TTMSS (BDE(Si-H) = 84 kcal/mol, Table 1.1) to form an ethane (BDE(Et-H) = 101 kcal/mol, Table 1.1) and the radical chain carrier, (TMS)₃Si•, (Scheme 4.29). In the propagation phase, the silyl radical, (TMS)₃Si•, abstracts the bromine atom from 286 (for PhBr, BDE(C-Br) = 80 kcal/mol, Table 1.1) to form the aryl radical intermediate 317 and (TMS)₃SiBr (for TMS-Br, BDE(Si-Br) = 101 kcal/mol, Table 1.1). 317 then undergoes the 6-endo-trig radical cyclization to generate N-centered tetrahydrophthalazine radical 318, followed by HAT from TTMSS to afford the product 287, and to regenerate (TMS)₃Si•. The termination of the radical chain could occur in multiple pathways. One pathway is that different hydrogen atom sources, instead of TTMSS, quench the tetrahydrophthalazine radical 318, or the aryl radical 317. Another possible pathway is that (TMS)₃Si• is quenched by reacting with molecular oxygen or oxygen-centered radical species generated from triethylborane in the reaction.
Considering the hypothesis that triethylboranes could be coordinating with the C=N bonds of hydrazones (Section 4.4.3), we surmised that the radical cyclization may operate in an alternative radical chain mechanism, in which the ethyl radical serves as the radical chain carrier and is regenerated through the fragmentation of radical 321 after the 6-endo-trig radical cyclization onto the triethylborane-coordinated hydrazone 319 (Scheme 4.30).

**Scheme 4.29.** Proposed radical chain mechanism for the 6-endo-trig radical cyclization of hydrazone 286.
Mechanism 2

Initiation:

\[ \text{Et}_3\text{B} + \text{O}_2 \rightarrow \text{Et}\bullet + \text{Et}_2\text{B-}\text{O-O}\bullet \]

Propagation:

\[ \text{Et}\bullet + (\text{TMS})_3\text{SiH} \rightarrow \text{Et-H} + (\text{TMS})_3\text{Si}\bullet \]

\[ \begin{align*}
\text{Br} & \text{N} & \text{N} & \text{Boc} \\
\text{Ph} & & & \text{Et}_3\text{Si} \\
\text{319} & & & \\
\end{align*} \] + (TMS)$_3$Si• \[ \rightarrow \] 

\[ \begin{align*}
\text{Ph} & \text{N} & \text{N} & \text{Boc} \\
\text{Et}_3\text{Si} & & & \text{Br} \\
\text{320} & & & \\
\end{align*} \] 

\[ \begin{align*}
\text{320} & \rightarrow \text{6-endotrig radical cyclization} \rightarrow \\
\text{321} & \text{321} & \text{322} + \text{Et}\bullet \\
\end{align*} \]

Scheme 4.30. Proposed radical chain mechanism 2 for the 6-endo-trig radical cyclization onto triethylborane-coordinated hydrazone 286.

The radical cyclization step is considered to be irreversible, as a more stable nitrogen-centered hydrazyl radical (318 or 321, BDE(NH$_2$NH-H) = 81 kcal/mol, Table 1.1) is formed from an unstable aryl radical (BDE(Ph-H) = 113 kcal/mol, Table 1.1). Therefore, the diastereoselectivity of the radical cyclization is controlled kinetically and early transition states (TS) are involved. To explain the observed diastereoselectivity, we hypothesized that the 6-endo-trig radical cyclization process proceeds through boat transition states due to the conjugated systems of the hydrazones. Taking 312 as an example, in the boat TSs of the radical cyclization Me (R$^3$) can be at either the pseudo-axial or -equatorial positions. The other substituent, the phenyl ring (R$^2$) can be at either the pseudo-axial or -equatorial positions, from the starting Z- or
E-hydrazone aryl radical intermediates, **323a** and **323b** respectively (Figure 4.8). When Me (R³) is at the pseudo-axial position, TS1 and TS2 are possible for the cyclization with the phenyl substituent at pseudo-equatorial and axial positions respectively. When Me (R³) is at the pseudo-equatorial position, correspondingly TS3 and TS4 are possible for the cyclization. However we hypothesized that a significant 1,3-strain is generated between Me (R³) and the Boc group when Me (R³) is at the pseudo-equatorial position. Therefore, TS3 and TS4 are unfavored for the cyclization. In the comparison between TS1 and TS2, the former with phenyl group at the pseudo-equatorial position minimizes the steric interaction from Me (R³), while the latter has the phenyl and Me (R³) in spacial proximity to each other. Hence, TS1 is favored for the radical cyclization, and leads to *trans*-1,4-disubstituted tetrahydrophthalazines.

**Figure 4.8.** Two TSs proposed for the radical cyclization of hydrazone **312.**
4.4.5.2 Computational studies on the radical cyclization

To gain further insights into the energetics of this novel 6-endo-trig radical cyclization of hydrazones, we collaborated with Weiying He in the Kennepohl laboratory at the University of British Columbia for the computational studies on the diastereoselective radical cyclization processes. The theoretical calculations were performed using the open-shell B3LYP functional method in combination with the Ahlrichs double-ζ basis set with valence polarization for all atoms. The computational calculation was focused on the pathways involving the TS1 and TS2, since 1,3-strain formed between Me (R³) and the Boc group rendered TS3 and TS4 more unfavorable compared to the 1,4-steric interaction in TS1 and TS2. The calculated results showed that the optimized TSs of both pathways have boat conformations (Figure 4.9), similar to TS1 and TS2. Based on the computational results, both of the two reaction pathways have early TSs, and also have a significant energy difference between the two activation barriers, about 5 kcal/mol (Figure 4.10), which theoretically corresponds to >1000:1 diastereomeric ratio. These computational results agree with the our mechanistic hypotheses, and explain the excellent diastereoselectivity we observed in our experiments for the syntheses of 1,4-disubstituted tetrahydrophthalazines.
4.5 Conclusions

We have successfully developed a new 6-endo-trig radical cyclization of hydrazones and formulated two synthetic protocols using this radical cyclization method, including a one-pot process, for the syntheses of substituted tetrahydrophthalazines from readily available starting materials. These synthetic protocols proved to be high yielding and robust. Furthermore, a wide substrate scope was achieved, with good functional group tolerance. This radical cyclization provides the first method for the highly diastereoselective syntheses of trans-1,4-disubstituted
tetrahydrophthalazines. Overall, our approaches are able to address the challenges of controlling regio- and stereochemistry in the syntheses of phthalazine derivatives.

We proposed that the radical cyclization method operates in a radical chain mechanism, and the cyclization process has a boat transition state. The computational studies conducted in collaboration with the Kennepohl laboratory demonstrate that the high trans-diastereoselectivity obtained for the 1,4-disubstituted tetrahydrophthalazines is attributed to the large energy difference of the activation barriers of the two radical cyclization pathways.

4.6 Experimental information

General methods and instrumentation

Reagents and solvents were purchased from commercial sources and used as received, unless otherwise stated. Triethylborane (Et$_3$B) reagent was purchased as a 1.0 M solution in hexanes under inert atmosphere. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM) and N,N-dimethylformamide (DMF) were obtained by first sparging nitrogen gas through the solvents for one hour and then passing the solvents through activated alumina columns. Yields refer to chromatographically and spectroscopically homogeneous material, unless otherwise stated. The solid phase in the flash chromatography purification was Silicycle F60 silica gel (230-400 mesh).

A KD-Scientific KDS100 syringe pump was used for all slow additions. Infrared spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded using a Bruker AV-300 or 400 spectrometers. Low and high-resolution mass spectra were recorded on either a Bruker Esquire-LC spectrometer (LRMS) or a Waters/Micromass LCT spectrometer (for HRMS).
Syntheses of intermediates and hydrazones

\[
\begin{align*}
\text{Br} & \quad \text{HN}^\text{Boc} \quad \text{Br} \quad \text{HN}^\text{Boc} \\
\text{325} & \quad \text{NaH, TBAI} \\
\text{THF, 40 °C} & \quad \text{Br} \\
\text{289} & \quad \text{N}^\text{Boc} \quad \text{NH}_2
\end{align*}
\]

**tert-butyl 1-(2-bromobenzyl)hydrazine-1-carboxylate (289):** To a round bottom flask equipped with a stir bar and a mixture of Boc-hydrazide (1.32 g, 10 mmol) and tetrabutylammonium iodide (TBAI, 369 mg, 1.0 mmol) in anhydrous THF (0.25 M to hydrazide, 40 mL) was added sodium hydride (520 mg, 1.3 equiv, 60% dispersion in mineral oil) in portions. Once the gas evolution ceased, the reaction mixture was warmed up to 40 °C and a 1.0 M solution of \(\sigma\)-bromobenzyl bromide (325, 2.50 g, 10 mmol) in anhydrous THF was added dropwise. After the reaction was stirred at 40 °C for 4h, it was cooled down to room temperature and quenched by the slow addition of a saturated aq. NaHCO\(_3\) solution (20 mL). After dilution with water (20 mL), the mixture was extracted with EtOAc (50 mL). The combined organic phase was washed with brine (50 mL x 2), dried over sodium sulfate and concentrated *in vacuo* to get crude mixture which was purified via silica gel-based flash chromatography (10% to 80% EtOAc in hexanes) to afford alkylated hydrazide 289 (1.33 g) in 44% yield as a white solid.

**IR (neat):** 3334, 3222, 2976, 2922, 1685, 1427, 1398, 1352, 1251, 1167, 1109, 761 cm\(^{-1}\);

**\(^1\)H NMR** (300 MHz, CDCl\(_3\)): \(\delta\) 7.57 (dd, \(J = 7.8, 1.1\) Hz, 1 H), 7.37 - 7.29 (m, 1 H), 7.24 - 7.11 (m, 2 H), 4.70 (s, 2 H), 4.09 (br. s, 2 H), 1.49 (s, 9 H);

**\(^{13}\)C NMR** (75 MHz, CDCl\(_3\)): \(\delta\) 156.9, 137.0, 132.9, 128.6, 128.5, 127.4, 123.1, 81.1, 54.6, 28.4;

**HRMS-ESI(m/z):** calcd. for C\(_{12}\)H\(_7\)BrN\(_2\)NaO\(_2\) [M+Na\(^+\)] 323.0371, found 323.0373.
**tert-butyl-2-benzylidenehydrazine-1-carboxylate (326):** Procedure was performed as outlined by Gütschow and coworkers, and NMR data were found to be identical with literature values.

**$^1$H NMR** (300 MHz, CDCl$_3$) δ 7.89 (br. s, 1 H), 7.85 (s, 1 H), 7.72 - 7.69 (m, 2 H), 7.40 - 7.38 (m, 2 H), 1.56 (s, 9 H);

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 143.8, 134.0, 130.2, 129.9, 128.7, 127.3, 81.7, 28.4.

**tert-butyl \( (E) \)-2-(3-phenylpropyldiene)hydrazine-1-carboxylate (327):** Procedure was performed as outlined by Gütschow et al., and NMR data were found to be identical with those of the commercially available compound (CAS No.: 56572-29-3).

**$^1$H NMR** (300 MHz, CDCl$_3$) δ 7.84 (s, 1 H), 7.34 - 7.27 (m, 2 H), 7.25 - 7.16 (m, 3 H), 2.89 - 2.83 (m, 2 H), 2.63 (td, $J = 7.8$, 7.4, 5.4 Hz, 2 H), 1.52 (s, 9 H);

**$^{13}$C NMR** (101 MHz, CDCl$_3$) δ 152.6, 146.2, 140.7, 128.5, 128.4, 126.2, 81.1, 33.8, 32.9, 28.3.

**tert-butyl \( (E) \)-2-benzylidene-1-(2-bromobenzyl)hydrazine-1-carboxylate (286):** Following the procedure for the synthesis of 289, the reaction was run at 6.0 mmol scale to afford hydrazone 286 (2.42 g) in quantitative yield.
IR (film): 3064, 2988, 2956, 2924, 2854, 1730, 1695, 1466, 1439, 1396, 1367, 1347, 1332, 1246, 1210, 1148, 752, 693 cm⁻¹;

¹H NMR (300 MHz, CDCl₃) δ 7.66 - 7.60 (m, 3 H), 7.51 (br. s, 1 H), 7.39 - 7.32 (m, 3 H), 7.29 - 7.23 (m, 1 H), 7.18 - 7.12 (m, 1 H), 7.07 (d, J = 7.5 Hz, 1 H), 5.18 (s, 2 H), 1.61 (s, 9 H);

¹³C NMR (75 MHz, CDCl₃) δ 153.7, 141.0, 135.0, 134.5, 133.1, 129.6, 129.0, 128.7, 128.0, 127.5, 127.3, 122.3, 82.4, 48.5, 28.4;

HRMS-ESI(m/z): calcd. for C₁₉H₂₂BrN₂O₂ [M+H]⁺ 389.0865, found 389.0867.

tert-butyl (E)-2-benzylidene-1-(2-bromo-4-fluorobenzyl)hydrazine-1-carboxylate (330): To a 0.4 M solution of 2-bromo-4-fluorobenzaldehyde (328, 609 mg, 3.0 mmol) in MeOH (7.5 mL) was added sodium borohydride (136 mg, 3.6 mmol) in one portion at 0 °C. The reaction was then stirred at room temperature for 1 h before concentrated in vacuo to get crude mixture. The crude mixture was diluted with ethyl acetate (30 mL) and then washed with saturated aq. NH₄Cl solution (20 mL) and brine (20 mL x 2), dried over sodium sulfate and concentrated in vacuo to get the corresponding benzyl alcohol product (609 mg) in 99% yield, which did not require further purification.

The alcohol product (205 mg, 1 mmol) was dissolved in DCM (5.6 mL), to which was then added PBr₃ (0.19 mL, 2 equiv) as a liquid at room temperature. After being stirred at 42 °C for overnight, the reaction was then quenched with saturated aq. NaHCO₃ (30 mL) slowly and diluted with water (20 mL), and then extracted with ethyl acetate (30 mL x 3). The combined organic layer
was washed with brine (30 mL x 2), dried over sodium sulfate and concentrated *in vacuo* to get the product **329** (246 mg) in 92% yield as a clear liquid, which was utilized without further purification.

To a mixture of Boc-hydrazone **326** (193 mg, 0.88 mmol, 1.0 equiv) and tetrabutylammonium iodide (TBAI, 32.5 mg, 0.088 mmol) in anhydrous THF (2.5 mL, 0.35 M to hydrazone) was added sodium hydride (53 mg, 1.31 mmol, 60% dispersion in mineral oil) in portions. Once the gas evolution ceased, the reaction mixture was warmed up to 40 °C and a 0.5 M solution of 2-bromo-4-fluorobenzyl bromide (**329**, 0.92 mmol, 1.05 equiv) in anhydrous THF was added dropwise. After the reaction was stirred at 40 °C for overnight, it was cooled down to room temperature and quenched by slow addition of saturated aq. NaHCO₃ (10 mL). After dilution with water (10 mL), the mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine, dried over sodium sulfate and concentrated *in vacuo* to obtain a crude mixture, which was purified via silica gel-based flash chromatography (3% to 20% EtOAc in hexanes) to afford hydrazone **330** (314 mg) as a white solid in 88% yield.

**IR (film):** 3066, 2978, 2932, 1738, 1703, 1600, 1486, 1410, 1367, 1335, 1288, 1226, 1153, 863, 756, 694 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃) δ 7.66 - 7.64 (m, 2 H), 7.54 (br. s, 1 H), 7.39 - 7.32 (m, 4 H), 7.07 - 6.97 (m, 2 H), 5.14 (s, 2 H), 1.62 (s, 9 H);

**¹³C NMR** (101 MHz, CDCl₃) δ 162.8, 160.4, 153.5, 141.1, 134.8, 130.4, 129.6, 128.6, 128.5, 128.4, 127.2, 122.1, 122.0, 120.4, 120.1, 115.2, 115.0, 82.4, 47.9, 28.3;

**HRMS-ESI(m/z):** calcd. for C₁₉H₂₀BrFN₂NaO₂ [M+Na]⁺ 429.0590, found 429.0602.
**tert-butyl (E)-2-benzylidene-1-(2-bromo-4-methoxybenzyl)hydrazine-1-carboxylate (333):**

To a solution of acid 331 (2.00 g, 8.66 mmol) in anhydrous THF (22 mL) was added dimethyl sulfide borane complex (1.23 mL, 13.0 mmol) slowly at 0 °C. The mixture was then allowed to warm up to room temperature and stirred for overnight. The reaction was then quenched with saturated aq. NaHCO₃ (30 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine (50 mL x 2), dried over sodium sulfate before concentrated *in vacuo* to obtain the corresponding benzyl alcohol product (1.672 g) as clear colorless liquid in 89% yield, which was utilized without further purification.

The alcohol product (326 mg, 1.5 mmol) was dissolved in DCM (8.3 mL), to which was then added PBr₃ (0.28 mL, 2 equiv) in one portion at room temperature. After the reaction was stirred at 42 °C for overnight, it was then quenched with saturated aq. NaHCO₃ (45 mL) slowly and further diluted with water (30 mL), and then extracted with ethyl acetate (40 mL x 3). The combined organic layer was washed with brine (50 mL x 2), dried over sodium sulfate and concentrated *in vacuo* to get product 332 (359 mg) in 85% yield, which was utilized without further purification.

To a mixture of Boc-hydrazone 326 (282 mg, 1.28 mmol, 1.0 equiv) and tetrabutylammonium iodide (TBAI, 47 mg, 0.128 mmol) in anhydrous THF (0.35 M to hydrazone) was added sodium hydride (77 mg, 1.92 mmol, 60% dispersion in mineral oil) in portions. Once the gas evolution ceased, the reaction mixture was warmed up to 40 °C and a 0.5 M solution of 2-bromo-3-...
methoxybenzyl bromide (332, 359 mg, 1.28 mmol) in anhydrous THF was added dropwise. After the reaction was stirred at 40 °C for overnight, it was cooled down to room temperature and quenched by slow addition of saturated aq. NaHCO₃ (10 mL). After dilution with water (10 mL), the mixture was extracted with EtOAc (20 mL × 3). The combined organic phase was washed with brine (50 mL), dried over sodium sulfate and concentrated in vacuo to get crude mixture which was purified via silica gel-based flash chromatography (3% to 20% EtOAc in hexanes) to afford hydrazone 333 (477 mg) as a white solid in 89% yield.

**IR (film):** 3063, 2977, 2934, 2838, 1702, 1598, 1574, 1471, 1409, 1367, 1335, 1292, 1236, 1151, 894, 757, 694 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃) δ 7.65 (dd, J = 7.6, 1.8 Hz, 2 H), 7.52 (br. s, 1 H), 7.49 (d, J = 8.5 Hz, 1 H), 7.38 - 7.33 (m, 3 H), 6.71 (dd, J = 8.9, 3.1 Hz, 1 H), 6.63 (d, J = 3.1 Hz, 1 H), 5.14 (s, 2 H), 3.72 (s, 3 H) 1.62 (s, 9 H);

**¹³C NMR** (75 MHz, CDCl₃) δ 159.6, 153.5, 140.9, 135.5, 134.9, 133.6, 129.5, 128.5, 127.3, 114.6, 113.2, 112.4, 82.2, 55.4, 48.5, 28.3;

**HRMS-ESI(m/z):** calcd. for C₂₀H₂₃BrN₂O₃ [M+Na]⁺ 441.0790, found 441.0795.

![Chemical Reaction](image)

**tert-butyl (1,3-dio xoisoindolin-2-yl)carbamate (334):** Compound 334 was synthesized following the procedure outlined by Vanderesse and coworkers, and NMR data were found to be identical with the literature value.
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.95 - 7.92 (m, 2 H), 7.82 - 7.79 (m, 2 H), 6.56 (br. s, 1 H), 1.53 (br. s, 9 H);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 165.5, 153.4, 134.7, 130.0, 124.0, 83.2, 28.1.

**tert-butyl (E)-2-benzylidene-1-(2-bromo-4-morpholinobenzyl)hydrazine-1-carboxylate (336):** To a 0.048 M solution of 2-bromo-4-fluorobenzaldehyde (328, 1.70 g, 8.38 mmol) in 50% aqueous dioxane (174 mL) was added sulfamic acid (4.88 g, 50 mmol), sodium chlorite (986 mg, 10.9 mmol) and KH$_2$PO$_4$ (13.7 g, 101 mmol), and the mixture was stirred at room temperature overnight. The mixture was then concentrated *in vacuo*, diluted with water (40 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (100 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo* to afford acid product. The acid product was then dissolved in MeOH (10 mL) and was added concentrated H$_2$SO$_4$ (1 mL). The mixture was stirred at reflux overnight before cooled down to room temperature, diluted with water (40 mL) and extracted with DCM (40 mL x 3). The combined layer was then washed with water (100 mL) and brine (100 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo* to give ester 335 (1.74 g) in 89 % over two steps, which was utilized without further purification.

To a solution of 335 (558 mg, 2.4 mmol) in anhydrous DMF (4.8 mL) was added morpholine (1.04 mL, 12 mmol) at room temperature. The reaction was then stirred at 50 °C for overnight before cooled to room temperature. The reaction was diluted with aq. NaHCO$_3$ (40 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was then washed with water (50
mL x 2), 0.5 M aq. HCl (50 mL x 2) and brine (50 mL x 2), dried over sodium sulfate and concentrated *in vacuo* to give crude mixture. Purification via silica gel-based flash chromatography (3% to 30% EtOAc in petroleum ether) to afford product 336 as solid (441 mg) in 61% yield.

**IR (film):** 3056, 2954, 2919, 2851, 1718, 1594, 1501, 1433, 1381, 1300, 1269, 1226, 1115, 941 cm⁻¹;

**¹H NMR** (300 MHz, CDCl₃) δ 7.85 (d, *J* = 9.0 Hz, 1 H), 7.11 (d, *J* = 2.6 Hz, 1 H), 6.79 (dd, *J* = 8.7, 2.6 Hz, 1 H), 3.89 (s, 3 H), 3.87 - 3.81 (m, 4 H), 3.29 - 3.26 (m, 4 H);

**¹³C NMR** (101 MHz, CDCl₃) δ 165.8, 153.7, 133.2, 124.3, 120.3, 119.6, 112.3, 77.4, 77.1, 76.8, 66.5, 52.0, 47.4;

**HRMS-ESI*(m/z)*:** calcd. for C₁₂H₁₅NNaO₃ [M+H]⁺ 300.0235, found 300.0233.

**tert-buty** (E)-2-benzylidene-1-(2-bromo-4-morpholinobenzyl)hydrazine-1-carboxylate (338): To the solution of compound 336 (351 mg, 1.17 mmol) in anhydrous THF (4.7 mL) was added LiAlH₄ (44 mg, 1.17 mmol) in one portion at room temperature. The reaction was stirred at room temperature for 45 min before dilution with ether and cooled to 0 °C. The mixture was then quenched with water (0.044 mL) slowly and was further added 15% aq. NaOH solution (0.044 mL) and water (0.132 mL). The mixture was then warmed up to room temperature and stirred for 15 min before addition of anhydrous MgSO₄. After stirring for another 15 min, the
mixture was filtered and the filtrate was concentrated in vacuo to give the corresponding alcohol product in quantitative yield which was utilized without further purification. The alcohol product (188 mg, 0.69 mmol) was dissolved in anhydrous THF (3.5 mL) and was added hydrazide 334 (222 mg, 0.69 mmol), Ph3P (271 mg, 1.04 mmol) and diethyl azodicarboxylate (DEAD, 180 mg, 1.04 mmol) at 0 °C. The reaction was allowed to warm up to room temperature and stirred for overnight before concentrated in vacuo to give crude mixture. Purification by flash chromatography (10% to 60% EtOAc in hexanes) afforded product 337 (225 mg) as a yellowish solid in 63% yield. The product was then directly dissolved in THF (2.6 mL) and treated with hydrazine hydrate (84 mg, 1.31 mmol) at 0 °C. The mixture was stirred at room temperature for overnight before filtered and concentrated in vacuo to give crude mixture. The crude mixture was directly dissolved in ethanol and was added benzaldehyde (69 mg, 1.5 equiv) and stirred at room temperature for overnight. Concentration in vacuo to give crude product and purification by flash chromatography (3% to 25% EtOAc in hexanes) to afford hydrazone 338 (80 mg) in 39% yield over two steps from 337.

**IR (film):** 3062, 2973, 2856, 2830, 1700, 1497, 1408, 1367, 1334, 1230, 1148, 1122, 940, 755, 694 cm\(^{-1}\);

**\(^1\)H NMR** (300 MHz, CDCl\(_3\)) \(\delta\) 7.65 (dd, \(J = 7.6, 2.2\) Hz, 2 H), 7.52 (s, 1 H), 7.38 - 7.31 (m, 3 H), 7.17 (d, \(J = 2.3\) Hz, 1 H), 6.96 (d, \(J = 8.7\) Hz, 1 H), 6.83 (dd, \(J = 8.6, 2.4\) Hz, 1 H), 5.12 (s, 2 H), 3.89 - 3.86 (m, 4 H), 3.18 - 3.14 (m, 4 H), 1.61 (s, 9 H);

**\(^13\)C NMR** (75 MHz, CDCl\(_3\)) \(\delta\) 153.7 151.4, 140.9, 134.9, 130.1, 129.4, 128.5, 127.9, 127.2, 122.9, 119.4, 115.1, 82.2, 66.7, 48.9, 47.8, 28.3;

**HRMS-ESI(m/z):** calcd. for C\(_{23}\)H\(_{28}\)BrN\(_3\)NaO\(_3\) [M+Na]\(^+\) 496.1212, found 496.1218.
1-\((\text{bromomethyl})\)-2-iodobenzene (341): Following the procedure for the synthesis of 332, 341 was synthesized as a brown solid (4.05 g) in 88% yield over two steps, and its characterization data match the literature value.²⁸⁰

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\) 7.88 (dd, \(J = 8.0, 0.9\) Hz, 1 H), 7.50 (dd, \(J = 7.5, 1.6\) Hz, 1 H), 7.36 (td, \(J = 7.4, 1.1\) Hz, 1 H), 7.01 (td, \(J = 7.7, 1.6\) Hz, 1 H), 4.63 (s, 2 H);

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)): \(\delta\) 140.2, 140.1, 130.5, 130.1, 128.9, 100.1, 38.8;

tert-butyl (Z)-1-(2-iodobenzyl)-2-(3-phenylpropylidene)hydrazine-1-carboxylate (342):

Following the procedure for the synthesis of 289, the title compound was afforded as a white solid (706 mg) in 76% yield.

\(\text{IR (film)}\): 3062, 3027, 2977, 2928, 2859, 1701, 1497, 1454, 1439, 1410, 1393, 1367, 1329, 1286, 1154, 1013, 747, 699 cm\(^{-1}\);

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)): \(\delta\) 7.86 (dd, \(J = 7.8, 1.1\) Hz, 1 H), 7.33 - 7.29 (m, 2 H), 7.25 - 7.14 (m, 3 H), 7.09 - 7.03 (m, 2 H), 6.99 (td, \(J = 7.6, 1.7\) Hz, 1 H), 6.90 (d, \(J = 7.8\) Hz, 1 H), 6.75 (t, \(J = 4.8\) Hz, 1 H), 4.87 (s, 2 H), 2.80 - 2.71 (m, 2 H), 2.65 - 2.55 (m, 2 H), 1.55 (s, 9 H);

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)): \(\delta\) 153.6, 144.9, 140.9, 139.7, 137.1, 129.1, 128.7, 128.6, 126.9, 126.1, 97.1, 82.2, 53.6, 34.8, 33.2, 28.4;
**HRMS-ESI(m/z):** calcd. for C_{21}H_{25}IN_{2}NaO_{2}[M+Na]^+ 487.0862, found 487.0858.

**tert-butyl (Z)-1-(2-bromobenzyl)-2-(pent-4-en-1-ylidene)hydrazine-1-carboxylate (345):** To a suspension with pyridinium chlorochromate (PCC, 808 mg) and a scoop of celite in DCM (5 mL) under nitrogen atmosphere at room temperature was added alcohol 343 in one portion. The mixture with a dark brown color was stirred for 1.5 h before filtered through a silica gel and celite cake and rinsed with more DCM (40 mL) to afford colorless clear filtrate solution. This solution was added hydrazide 289 (335 mg) in one portion and sodium sulfate, and was stirred at room temperature for overnight. Then it was filtered and concentrated in vacuo to get crude product, which was further purified via silica gel-based flash chromatography (0% to 20% ether in hexanes) to afford hydrazone 345 as a white solid (373 mg) in 41% yield over two steps.

**IR (film):** 3068, 2978, 2931, 1703, 1469, 1443, 1410, 1393, 1367, 1249, 1154, 1027, 750 cm⁻¹;

**¹H NMR** (300 MHz, CDCl₃): δ 7.57 (dd, J = 7.9, 1.3 Hz, 1 H), 7.31 - 7.23 (m, 2 H), 7.18 - 7.10 (m, 1 H), 6.99 (d, J = 6.9 Hz, 1 H), 6.81 (t, J = 4.9 Hz, 1 H), 5.81 - 5.66 (m, 1 H), 4.99 (s, 2 H), 4.96 - 4.92 (m, 1 H), 4.92 - 4.87 (m, 1 H), 2.43 - 2.33 (m, 2 H), 2.24 - 2.13 (m, 2 H), 1.55 (s, 9 H);

**¹³C NMR** (101 MHz, CDCl₃): δ 153.5, 145.2, 137.0, 134.4, 132.8, 128.7, 127.7, 127.3, 122.1, 115.5, 82.0, 48.4, 32.2, 30.9, 28.3;

**HRMS-ESI(m/z):** calcd. for C_{17}H_{23}BrN_{2}NaO_{2}[M+Na]^+ 389.0840, found 389.0841.
ethyl (E)-5-phenylpent-4-enoate (347): To a solution of benzaldehyde (2.03 mL, 20 mmol) in anhydrous THF (43 mL) under nitrogen atmosphere was added a 1.0 M solution of vinyl magnesium bromide in THF (24 mL) at 0 °C slowly. The reaction was then allowed to warm up to room temperature and stirred for 2 h before quenched with water and diluted with 1.0 M aq. solution of HCl (20 mL). The mixture was extracted with EtOAc (80 mL x 3). The combine organic layer was washed with brine (50 mL x 2), dried over sodium sulfate and concentrated in vacuo to afford 346 as a yellowish clear liquid (2.65 g) in 99% yield. 346 (1.34 g, 10 mmol) was then dissolved in triethyl orthoacetate (18.2 mL) and was added propionic acid (7.4 mg, 0.1 mmol). The reaction was stirred at reflux for 42 h before concentrated in vacuo to afford crude product. The crude product was washed successively with 1.0 M aq HCl solution (30 mL x 2), water (30 mL) and brine (30 mL), dried over sodium sulfate and concentrated in vacuo to get product (347, 2.04 g) as a yellowish clear liquid in quantitative yield. The characterization data match the literature value.\\(^{281}\)

\[\text{H NMR (300 MHz, CDCl}_3\): 8 7.42 -7.30 (m, 4 H), 7.24 – 7.22 (m, 1 H), 6.46 (d, \(J = 16.0\) Hz, 1 H), 6.23 (dt, \(J = 16.0, 6.4\) Hz, 1 H), 4.17 (q, \(J = 7.2\) Hz, 2 H), 2.59 – 2.48 (m, 4 H), 1.28 (t, \(J = 7.2\) Hz, 3 H);}

\[\text{C NMR (101 MHz, CDCl}_3\): 8 173.3, 138.9, 131.1, 128.7, 128.6, 127.3, 126.2, 60.6, 34.2, 28.8, 14.4.}
(E)-5-phenylpent-4-enal (349): To the suspension of LiAlH₄ (LAH, 223 mg, 5.9 mmol) in anhydrous Et₂O (12.5 mL) was added a 1.0 M solution of ester 348 (1.02 g, 5.0 mmol) in anhydrous Et₂O slowly at 0 °C. The mixture was stirred at 0 °C for 2.5h before quenched with water (1 mL), and further added 15% aq NaOH (1 mL) and water (1 mL). The mixture was filtered through silica gel pad, dried over Na₂SO₄ and concentrated in vacuo. The crude product was then directly dissolved in anhydrous DCM (75 mL) and was added NaOAc (410 mg, 5.0 mmol), NaHCO₃ (420 mg, 5.0 mmol) and celite (3.5 g). Then pyridinium chlorochromate (PCC, 3.24 g, 15 mmol) was added to the reaction mixture as a solid in two portions. After stirring for overnight, the reaction was filtered through a celite/silica gel cake and concentrated in vacuo to give the crude product. Further purification via silica gel-based flash chromatography (0% to 30% Et₂O in hexanes) afforded the aldehyde 349 (165 mg) in 20% yield overall. The NMR characterization data match the literature value.²⁸²

**¹H NMR** (300 MHz, CDCl₃): δ 9.85 (t, J = 1.4 Hz, 1 H), 7.40 - 7.20 (m, 5 H), 6.46 (d, J = 15.8 Hz, 1 H), 6.23 (dt, J = 15.8, 6.5 Hz, 1 H), 2.49 - 2.73 (m, 4 H);

**¹³C NMR** (101 MHz, CDCl₃): δ 173.3, 138.9, 131.1, 128.7, 128.6, 127.3, 126.2, 60.6, 34.2, 28.8, 14.3.
Conversion determination in the optimization of the radical cyclization

Hydrazone 286 was used as substrate in condition optimization with reactions run at 0.1 mmol scale. After running under designated conditions, reactions were concentrated *in vacuo* to give crude mixture. Analysis of the crude mixture via \(^1\)H NMR spectroscopy gives the conversion of substrate to desired product 287.

Taking entry 7 (manuscript Table 1) as example, \(^1\)H NMR of crude mixture was shown below: Ratio of H\(_a\) (286) and H\(_b\) (287) integration is 5.74/2.00, which gives the conversion of 286 to 287 to be 85%.

![Figure 4.11. \(^1\)H NMR spectrum of crude reaction mixture of 286 for entry 4, in Table 4.2.](image)
**General procedures for the syntheses of tetrahydraphthalazines**

A. **One-pot procedure (condensation/radical cyclization):**

To a 0.2 M solution of hydrazide 289 in EtOH was added an aldehyde (1.0 equiv) in one portion. After stirring at room temperature for overnight, the solvent was removed by rotary evaporation in ~30min to afford benzylated hydrazone quantitatively. The resulted hydrazone was then dissolved in toluene to form a 0.02 M solution, to which was further added reagent (TMS)$_3$SiH (2.5 equiv) and a 1.0 M solution of Et$_3$B (5.0 equiv) in hexane at room temperature. The reaction was stirred in air atmosphere at room temperature and monitored by TLC till it was finished (reaction time 0.5h to 3h). After completion, the reaction was concentrated *in vacuo* to get crude mixture, which was purified by silica gel-based flash chromatography (solvent systems: EtOAc or Et$_2$O/hexanes, or MeOH/DCM) to afford the tetrahydrophthalazine product.

B. **Hydrazone radical cyclization:**

The requisite benzylated hydrazone was dissolved in toluene to form a 0.02 M solution, to which was further added reagent (TMS)$_3$SiH (2.5 equiv) and a 1.0 M solution of Et$_3$B (5.0 equiv) in hexanes at room temperature. The reaction was stirred in air atmosphere at room temperature and monitored by TLC till it was finished (reaction time 0.5 h to 3 h). After completion, the reaction was concentrated *in vacuo* to get crude mixture, which was purified by silica gel based flash
chromatography (solvent systems: EtOAc/hexanes or MeOH/DCM) to afford the tetrahydrophthalazine product.

![Image of tetrahydrophthalazine product](287)

**tert-butyl 4-phenyl-3,4-dihydrophthalazine-2(1H)-carboxylate (287):** Following one-pot procedure A, reaction was run on 1.0 mmol scale for 1.5h and compound 287 was obtained in 85% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).

**IR (film):** 3292, 3063, 3028, 2976, 2929, 2850, 1688, 1491, 1453, 1367, 1236, 1164, 1119, 745, 700 cm\(^{-1}\);

**\(^1\)H NMR (300 MHz, CDCl\(_3\)):** \(\delta 7.40 - 7.24 (m, 6 \text{ H}), 7.24 - 7.18 (m, 1 \text{ H}), 7.15 (t, J = 7.3 \text{ Hz}, 1 \text{ H}), 6.88 (d, J = 7.4 \text{ Hz}, 1 \text{ H}), 5.25 (s, 1 \text{ H}), 5.17 (br. s, 1 \text{ H}), 4.90 - 4.80 (m, 2 \text{ H}), 1.41 (s, 9 \text{ H});

**\(^{13}\)C NMR (101 MHz, CDCl\(_3\)):** \(\delta 154.7, 140.8, 136.7, 132.6, 129.4, 128.4, 128.1, 128.0, 126.9, 126.4, 125.9, 80.9, 62.0, 46.3, 28.3;

**HRMS-ESI(\(m/z\)):** calcd. for C\(_{19}\)H\(_{23}\)N\(_2\)O\(_2\) [M+H]\(^+\) 311.1760, found 311.1756.
tert-butyl 4-(4-(tert-butyl)phenyl)-3,4-dihydrophthalazine-2(1H)-carboxylate (290):
Following one-pot procedure A, reaction was run on 0.30 mmol scale for 1.75h and compound 290 (88 mg) in 80% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).

IR (film): 3216, 3007, 2966, 2905, 2869, 1683, 1477, 1454, 1382, 1366, 1237, 1164, 1120, 819, 747 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): δ 7.38 - 7.34 (m, 2 H), 7.28 - 7.13 (m, 5 H), 6.91 (d, J = 7.7 Hz, 1 H), 5.21 (s, 1 H), 4.98 (br. s, 1 H), 4.91 - 4.75 (m, 2 H), 1.38 (br. s, 9 H), 1.34 (s, 9 H);

¹³C NMR (75 MHz, CDCl₃): δ 154.6, 150.8, 136.6, 132.6, 129.0, 128.1, 126.8, 126.3, 125.9, 125.3, 80.7, 61.6, 46.0, 34.6, 31.4, 28.3;


tert-butyl 4-(4-fluorophenyl)-3,4-dihydrophthalazine-2(1H)-carboxylate (291): Following one-pot procedure A, reaction was run on 0.30 mmol scale for 1.5h and compound 291 (92 mg) was obtained in 94% yield after purification by flash chromatography (2% to 40% Et₂O in hexanes).
IR (film): 3293, 3068, 3007, 2979, 2931, 2851, 1684, 1508, 1454, 1366, 1224, 1156, 1120, 825, 746 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): δ 7.29 - 7.24 (m, 3 H), 7.21 - 7.13 (m, 2 H), 7.07 - 6.99 (m, 2 H), 6.85 (d, J = 7.5 Hz, 1 H), 5.22 (s, 1 H), 4.87 - 4.76 (m, 2 H), 1.42 (s, 9 H);

¹³C NMR (75 MHz, CDCl₃): δ 164.2, 160.9, 154.6, 136.7, 132.5, 131.0, 130.9, 127.9, 127.0, 126.5, 126.0, 115.4, 115.1, 80.9, 61.1, 46.2, 28.3

HRMS-EI(m/z): calcd. for C₁₉H₂₁FN₂O₂ [M⁺] 328.1587, found 328.1583.

**t**-butyl 4-(4-chlorophenyl)-3,4-dihydrophthalazine-2(1H)-carboxylate (292): Following one-pot procedure A, reaction was run on 0.32 mmol scale for 1.5h and Compound 292 (95 mg) was obtained in 85% yield (86% total yield contaminated with 1 mass % EtOAc) after purification by flash chromatography (3% to 20% EtOAc in hexanes).

IR (film): 3289, 3065, 2977, 2931, 2848, 1689, 1489, 1454, 1368, 1237, 1165, 1121, 1091, 818, 746 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): δ 7.34 - 7.30 (m, 2 H), 7.27 - 7.13 (m, 5 H), 6.84 (d, J = 7.7 Hz, 1 H), 5.22 (s, 1 H), 4.88 - 4.75 (m, 2 H), 1.41 (s, 9 H);

¹³C NMR (101 MHz, CDCl₃): δ 154.6, 139.4, 133.9, 132.5, 130.7, 130.4, 128.6, 127.9, 127.1, 126.5, 126.0, 81.0, 61.2, 46.2, 28.3

tert-butyl 4-(4-cyanophenyl)-3,4-dihydrophthalazine-2(1H)-carboxylate (293): Following one-pot procedure A, reaction was run on 0.40 mmol scale for 3h and Compound 293 (116 mg) was obtained in 85% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).

IR (film): 3281, 3065, 2977, 2929, 2855, 2229, 1686, 1481, 1454, 1368, 1237, 1165, 1124, 822, 751 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 7.61\ (d, J = 8.1 \text{ Hz}, 2 \text{ H}), 7.40\ (d, J = 8.1 \text{ Hz}, 2 \text{ H}), 7.30 - 7.26\ (m, 1 \text{ H}), 7.21 - 7.13\ (m, 2 \text{ H}), 6.81\ (d, J = 7.8 \text{ Hz}, 1 \text{ H}), 5.27\ (s, 1 \text{ H}), 4.86\ (d, J = 16.5 \text{ Hz}, 1 \text{ H}), 4.72\ (d, J = 16.5 \text{ Hz}, 1 \text{ H}), 1.37\ (s, 9 \text{ H});

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 154.7, 146.3, 132.6, 132.3, 130.2, 128.0, 127.6, 126.9, 126.4, 118.8, 112.0, 81.4, 61.4, 46.2, 28.4;

HRMS-ESI(m/z): calcd. for C\(_{20}\)H\(_{21}\)N\(_3\)NaO\(_2\) [M+Na]\(^+\) 358.1531, found 358.1533.

tert-butyl 4-((methoxycarbonyl)phenyl)-3,4-dihydrophthalazine-2(1H)-carboxylate (294):

Following one-pot procedure A, reaction was run on 0.30 mmol scale for 2h and compound 294

164
(87 mg) was obtained in 79% yield after purification by flash chromatography (4% to 50% EtOAc in hexanes).

**IR (film):** 3290, 3065, 3006, 2978, 2848, 1719, 1688, 1480, 1436, 1367, 1277, 1237, 1164, 1106, 1091, 828, 746 cm⁻¹;

**¹H NMR** (300 MHz, CDCl₃): δ 8.01 - 7.99 (m, 2 H), 7.37 (d, J = 8.2 Hz, 2 H), 7.28 - 7.25 (m, 1 H), 7.21 - 7.19 (m, 1 H), 7.14 (t, J = 7.5 Hz, 1 H), 6.82 (d, J = 7.2 Hz, 1 H), 5.29 (s, 1 H), 4.88 - 4.77 (m, 2 H), 3.92 (s, 3 H) 1.38 (s, 9 H);

**¹³C NMR** (101 MHz, CDCl₃): δ 167.0, 154.7, 146.0, 135.8, 132.6, 129.9, 129.8, 129.5, 128.1, 127.3, 126.7, 126.2, 81.2, 61.7, 52.2, 46.2, 28.4;

**HRMS-ESI(m/z):** calcd. for C₂₁H₂₄N₂NaO₄ [M+Na]⁺ 391.1634, found 391.1632.

**tert-butyl 4-(2,3-dichlorophenyl)-3,4-dihydrophthalazine-2(1H)-carboxylate (295):**

Following one-pot procedure A, reaction was run on 0.30 mmol scale for 1.5h and compound 295 (105 mg) was obtained in 92% yield after purification by flash chromatography (3% to 24% Et₂O in hexanes).

**IR (film):** 3286, 3068, 3008, 2979, 2931, 2853, 1690, 1477, 1449, 1421, 1385, 1367, 1239, 1154, 1121, 747 cm⁻¹;
\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.39 (d, \(J = 8.0\) Hz, 1 H), 7.32 - 7.15 (m, 3 H), 7.01 (t, \(J = 7.9\) Hz, 1 H), 6.91 (d, \(J = 7.5\) Hz, 1 H), 6.59 (br. s, 1 H), 5.66 (s, 1 H), 5.02 (d, \(J = 15.8\) Hz, 1 H), 4.59 (d, \(J = 15.8\) Hz, 1 H), 1.21 (s, 9 H);

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 153.8, 141.4, 133.3, 133.2, 133.1, 129.9, 129.3, 128.2, 127.7, 127.0, 126.8, 126.3, 80.9, 59.0, 45.3, 28.2;

HRMS-EI(m/z): calcd. for C\(_{19}\)H\(_{20}\)Cl\(_2\)N\(_2\)O\(_2\) [M]\(^+\) 378.0902, found 378.0894.

**tert-butyl 4-(perfluorophenyl)-3,4-dihydropthalazine-2(1H)-carboxylate (296):** Following one-pot procedure \(\mathcal{A}\), reaction was run on 0.20 mmol scale for 2h and compound 296 (57 mg) was obtained in 71% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).

IR (film): 3284, 3066, 2979, 2932, 1686, 1521, 1499, 1384, 1367, 1237, 1162, 1121, 993, 752 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.32 - 7.27 (m, 1 H), 7.22 - 7.15 (m, 2 H), 6.87 (d, \(J = 7.8\) Hz, 1 H), 5.67 (s, 1 H), 5.01 (br. s, 1 H), 4.82 (s, 2 H), 1.46 (s, 9 H);

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 154.6, 147.4, 144.0, 142.8 139.3, 136.0, 133.5, 132.4, 127.5, 126.8, 126.2, 126.1, 114.4, 81.4, 51.9, 46.1, 28.2

HRMS-ESI(m/z): calcd. for C\(_{19}\)H\(_{17}\)F\(_5\)N\(_2\)NaO\(_2\) [M+Na]\(^+\) 423.1108, found 423.1114.
tert-butyl 4-(3-cyanophenyl)-3,4-dihydrophthalazine-2(1H)-carboxylate (297): Following one-pot procedure A, reaction was run on 0.40 mmol scale for 3h and compound 297 (123 mg) was obtained in 92% yield after purification by flash chromatography (3% to 25% EtOAc in hexanes).

IR (film): 3281, 3067, 3008, 2978, 2931, 2853, 2230, 1683, 1480, 1454, 1367, 1236, 1163, 1122, 864, 747 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.61 - 7.55 (m, 3 H), 7.45 - 7.40 (m, 1 H), 7.31 - 7.26 (m, 1 H), 7.22 - 7.14 (m, 2 H), 6.82 (d, $J$ = 7.5 Hz, 1 H), 5.24 (s, 1 H), 4.86 (d, $J$ = 16.5 Hz, 1 H), 4.70 (d, $J$ = 16.5 Hz, 1 H), 4.59 (br. s, 1 H), 1.37 (s, 9 H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 154.7, 142.7, 135.1, 133.9, 133.0, 132.6, 131.7, 129.3, 128.0, 127.6, 126.9, 126.5, 118.8, 112.6, 81.3, 61.1, 46.2, 28.4;

HRMS-ESI($m/z$): calcd. for C$_{20}$H$_{21}$N$_3$NaO$_2$ [M+Na]$^+$ 358.1531, found 358.1530.

tert-butyl 4-(pyridin-3-yl)-3,4-dihydrophthalazine-2(1H)-carboxylate (298): Following one-pot procedure A, reaction was run on 0.40 mmol scale for 30 min and compound 298 (88 mg) was
obtained in 70% yield after purification by flash chromatography (20% to 100% EtOAc in hexanes).

**IR (film):** 3273, 3029, 3003, 2977, 2929, 2855, 1689, 1577, 1478, 1454, 1425, 1383, 1367, 1237, 1165, 1126, 748, 713 cm$^{-1}$;

**$^1$H NMR (400 MHz, CDCl$_3$):** δ 8.57 (d, $J = 7.5$ Hz, 2 H), 7.55 (s, 1 H), 7.28 - 7.25 (m, 2 H) 7.21 - 7.19 (m, 1 H), 7.15 (t, $J = 7.5$ Hz, 1 H), 6.83 (d, $J = 7.2$ Hz, 1 H), 5.25 (s, 1 H), 4.97 (br. s, 1 H), 4.85 (d, $J = 16.0$ Hz, 1 H), 4.70 (d, $J = 16.0$ Hz, 1 H), 1.37 (s, 9 H);

**$^{13}$C NMR (101 MHz, CDCl$_3$):** δ 154.7, 150.7, 149.3, 136.8, 136.7, 132.7, 128.0, 127.4, 126.8, 126.3, 123.6, 123.5, 81.2, 59.5, 46.1, 28.4;

**HRMS-ESI(m/z):** calcd. for C$_{18}$H$_{21}$N$_3$NaO$_2$ [M+Na]$^+$ 334.1531, found 334.1534.

*tert*-butyl 4-(pyridin-2-yl)-3,4-dihyrophthalazine-2(1H)-carboxylate (299): Following one-pot procedure $A$, reaction was run on 0.36 mmol scale for 30 min and compound 299 (110 mg) was obtained in 98% yield after purification by flash chromatography (0% to 10% MeOH in DCM).

**IR (film):** 3291, 3065, 3007, 2978, 2931, 1688, 1589, 1473, 1454, 1435, 1388, 1367, 1236, 1163, 1123, 743 cm$^{-1}$;
**\(^1\)H NMR** (300 MHz, CDCl\(_3\)): \(\delta\) 8.65 - 8.64 (m, 1 H), 7.61 (td, \(J = 7.7\) Hz, 1 H), 7.30 - 7.15 (m, 4 H), 7.08 (d, \(J = 7.7\) Hz, 1 H), 6.97 (d, \(J = 7.7\) Hz, 1 H), 5.38 (s, 1 H), 5.30 (br. s, 1 H), 4.91 (d, \(J = 16.2\) Hz, 1 H), 4.75 (d, \(J = 16.2\) Hz, 1 H), 1.35 (s, 9 H);

**\(^13\)C NMR** (101 MHz, CDCl\(_3\)): \(\delta\) 160.6, 154.2, 149.5, 136.5, 132.5, 128.0, 127.2, 126.6, 126.2, 123.4, 122.7, 80.7, 63.1, 45.9, 28.2;

**HRMS-EI(m/z):** calcd. for C\(_{18}\)H\(_{21}\)N\(_3\)O\(_2\) [M]+ 311.1634, found 311.1629.

**tert-butyl 4-(furan-2-yl)-3,4-dihydrophthalazine-2(1H)-carboxylate (300):** Following one-pot procedure A, reaction was run on 0.20 mmol scale for 40 min and Compound 300 (40 mg) was obtained in 67% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).

**IR (film):** 3290, 3116, 3066, 2924, 2854, 1691, 1480, 1454, 1391, 1369, 1239, 1168, 1124, 745 cm\(^{-1}\);

**\(^1\)H NMR** (300 MHz, CDCl\(_3\)): \(\delta\) 7.43 (dd, \(J = 1.7\), 0.8 Hz, 1 H), 7.32 - 7.27 (m, 2 H), 7.23 - 7.18 (m, 2 H), 7.09 (d, \(J = 7.3\) Hz, 1 H), 6.30 (dd, \(J = 3.2\), 1.8 Hz, 1 H), 5.98 (s, 1 H), 5.29 (s, 1 H), 4.96 (d, \(J = 16.9\) Hz, 1 H), 4.61 (d, \(J = 16.9\) Hz, 1 H), 1.40 (s, 9 H);

**\(^13\)C NMR** (101 MHz, CDCl\(_3\)): \(\delta\) 154.3, 154.0, 142.5, 133.2, 132.4, 127.9, 127.4, 126.4, 126.1, 110.3, 109.7, 80.9, 55.2, 45.4, 28.2;

**HRMS-EI(m/z):** calcd. for C\(_{17}\)H\(_{20}\)N\(_2\)NaO\(_3\) [M]+ 323.1372, found 323.1368.
**tert-butyl 4-phenethyl-3,4-dihydropthalazine-2(1H)-carboxylate (301):** Following one-pot procedure A, reaction was run on 0.30 mmol scale for 1.5h and compound 301 (85 mg) was obtained in 84% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).

**IR (film):** 3277, 3025, 2975, 2920, 2850, 1686, 1496, 1454, 1390, 1366, 1238, 1168, 1126, 745 cm\(^{-1}\);

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):** δ 7.34 - 7.28 (m, 4 H), 7.25 - 7.18 (m, 3 H), 7.14 - 7.08 (m, 2 H), 4.92 (d, \(J = 16.5\) Hz, 1 H), 4.49 (d, \(J = 16.5\) Hz, 1 H), 4.33 (br. s, 1 H), 3.99 (d, \(J = 9.2\) Hz, 1 H), 3.13 - 3.06 (m, 1 H), 2.94 - 2.87 (m, 1 H), 2.15 - 2.05 (m, 1 H), 2.01 - 1.93 (m, 1 H), 1.56 (s, 9 H);

**\(^{13}\)C NMR (101 MHz, CDCl\(_3\)):** δ 155.4, 142.2, 137.7, 131.7, 128.5, 128.4, 126.6, 126.4, 126.3, 125.8, 80.7, 57.2, 45.7, 36.5, 32.7, 28.5;


**tert-butyl 4-benzyl-3,4-dihydropthalazine-2(1H)-carboxylate (302):** Following one-pot procedure A, reaction was run on 0.21 mmol scale for 1.5h and compound 302 (56 mg) was obtained in 82% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).
**IR (film):** 3286, 3063, 3025, 2976, 2926, 1687, 1496, 1454, 1382, 1366, 1232, 1165, 1123, 751 cm$^{-1}$;

**$^1$H NMR (300 MHz, CDCl$_3$):** $\delta$ 7.36 (d, $J$ = 4.4 Hz, 4 H), 7.30 - 7.11 (m, 5 H), 4.80 (d, $J$ = 16.4 Hz, 1 H), 4.63 (d, $J$ = 16.4 Hz, 1 H), 4.32 (dd, $J$ = 9.3, 4.5 Hz, 1 H), 3.19 (dd, $J$ = 14.0, 4.5 Hz, 1 H), 3.01 (dd, $J$ = 14.0, 9.3 Hz, 1 H), 1.47 (s, 9 H);

**$^{13}$C NMR (75 MHz, CDCl$_3$):** $\delta$ 154.9, 138.5, 136.9, 132.2, 129.4, 128.6, 126.7, 126.6, 126.3, 126.2, 80.8, 58.6, 46.3, 40.8, 28.3;

**HRMS-ESI(m/z):** calcd. for C$_{20}$H$_{25}$N$_2$O$_2$ [M+H]$^+$ 325.1916, found 325.1916.

**tert-butyl 4-hexyl-3,4-dihydropthalazine-2(1H)-carboxylate (303):** Following one-pot procedure $\mathcal{A}$, reaction was run on 0.305 mmol scale for 1.5h and compound 303 (77 mg) was obtained in 80% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).

**IR (film):** 3279, 3056, 2976, 2856, 1689, 1492, 1454, 1389, 1366, 1236, 1170, 1127, 746 cm$^{-1}$;

**$^1$H NMR (300 MHz, CDCl$_3$):** $\delta$ 7.27 - 7.19 (m, 2 H), 7.14 - 7.09 (m, 2 H), 4.84 (d, $J$ = 16.5 Hz, 1 H), 4.50 (d, $J$ = 16.5 Hz, 1 H), 4.10 (br. s, 1 H), 3.96 (d, $J$ = 7.9 Hz, 1 H), 1.75 - 1.68 (m, 2 H), 1.52 (s, 9 H), 1.36 - 1.32 (m, 8 H), 0.90 (t, $J$ = 6.5 Hz, 3 H);

**$^{13}$C NMR (101 MHz, CDCl$_3$):** $\delta$ 155.3, 138.2, 131.8, 126.6, 126.5, 126.5, 126.3, 80.7, 56.0, 45.9, 34.9, 31.9, 29.5, 28.6, 26.7, 22.8, 14.2;

**HRMS-ESI(m/z):** calcd. for C$_{25}$H$_{32}$N$_2$O$_2$ [M+H]$^+$ 319.2380, found 319.2396.
**tert-butyl 4-cyclohexyl-3,4-dihydrophthalazine-2(1H)-carboxylate (304):** Following one-pot procedure A, reaction was run on 0.30 mmol scale for 1.75h and compound 304 (92 mg) was obtained in 95% yield (96% total yield contaminated with 0.6 mass % DCM) after purification by flash chromatography (3% to 40% Et₂O in hexanes).

**IR (film):** 3276, 3065, 3006, 2977, 2922, 2851, 1683, 1493, 1451, 1388, 1365, 1237, 1168, 1125, 826, 748 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.26 - 7.17 (m, 2 H), 7.15 - 7.11 (m, 2 H), 4.84 (d, J = 16.5 Hz, 1 H), 4.47 (d, J = 16.5 Hz, 1 H), 4.09 (br. s, 1 H), 3.72 (s, 1 H), 2.11 (br. s, 1 H), 1.78 (br. s, 2 H), 1.68 (br. s, 2 H), 1.55 (s, 9 H), 1.39 - 1.09 (m, 6 H);

**¹³C NMR** (101 MHz, CDCl₃): δ 155.3, 136.4, 132.0, 127.4, 126.6, 126.5, 125.7, 80.6, 62.9, 41.1, 30.7, 28.5, 26.8, 26.6, 26.5;

**HRMS-ESI(m/z):** calcd. for C₁₉H₂₉N₂O₂ [M+H]⁺ 317.2229, found 317.2232.

**tert-butyl 4-(tert-butyl)-3,4-dihydrophthalazine-2(1H)-carboxylate (305):** Following one-pot procedure A, reaction was run on 0.40 mmol scale for 1.5h and compound 305 (104 mg) was obtained in 90% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).
IR (neat): 3300, 3051, 3030, 2979, 2949, 2865, 1665, 1492, 1445, 1395, 1368, 1169, 1133, 754, 734 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): δ 7.28 - 7.20 (m, 1 H), 7.17 - 7.14 (m, 3 H), 4.82 (d, J = 16.9 Hz, 1 H), 4.34 (d, J = 16.9 Hz, 1 H), 3.91 (br. s, 1 H), 3.59 (s, 1 H), 1.55 (s, 9 H), 1.05 (s, 9 H);

¹³C NMR (75 MHz, CDCl₃): δ 155.2, 135.4, 132.4, 128.7, 126.8, 126.6, 125.3, 80.5, 66.2, 45.2, 36.6, 28.6, 28.0;

HRMS-ESI(m/z): calcd. for C₁₇H₂₇N₂O₂ [M+H]⁺ 291.2073, found 291.2073.

***butyl 4-(but-3-en-1-yl)-3,4-dihydropthalazine-2(1H)-carboxylate (306):*** Following the cyclization procedure B, the reaction of hydrazone 346 was run on 0.4 mmol scale for 1.5 h and product 306 was obtained in 42% yield (48 mg) after purification by flash chromatography (3% to 20% EtOAc in hexanes).

IR (film): 3285, 3069, 2927, 2855, 1691, 1493, 1452, 1390, 1367, 1243, 1169, 1127, 834, 746, 688 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): δ 7.25 - 7.20 (m, 2 H), 7.15 - 7.12 (m, 2 H), 5.91 (ddt, J = 17.0, 10.4, 6.5 Hz, 1 H), 5.14 - 4.98 (m, 2 H), 4.90 (d, J = 16.7 Hz, 1 H), 4.46 (d, J = 16.4 Hz, 1 H), 3.99 (d, J = 6.9 Hz, 1 H), 2.58 - 2.41 (m, 1 H), 2.41 - 2.25 (m, 1 H), 1.94 - 1.67 (m, 2 H), 1.53 (s, 9 H);

¹³C NMR (75 MHz, CDCl₃): δ 155.3, 138.3, 137.8, 131.7, 126.6, 126.44, 126.41, 126.3, 115.0, 80.7, 57.2, 45.5, 33.9, 30.7, 28.4;
**HRMS-ESI(m/z):** calcd. for C$_{17}$H$_{24}$N$_2$NaO$_2$ [M+Na]$^+$ 311.1735, found 311.1734.

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**tert-butyl (E)-4-(4-phenylbut-3-en-1-yl)-3,4-dihydropthalazine-2(1H)-carboxylate (307):**

Following one-pot procedure A, reaction was run on 0.30 mmol scale for 30 min and compound 307 (83 mg) was obtained in 74% yield (76% total yield contaminated with 2 mass % DCM) after purification by flash chromatography (3% to 20% EtOAc in hexanes).

**IR (film):** 3281, 3061, 3025, 2975, 2927, 2852, 1687, 1493, 1451, 1389, 1366, 1238, 1165, 1125, 965, 735, 693 cm$^{-1}$;

**$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 7.39 - 7.31 (m, 4 H), 7.26 - 7.19 (m, 3 H), 7.17 - 7.13 (m, 2 H), 6.51 (d, $J = 15.7$ Hz, 1 H), 6.32 (dt, $J = 15.7$, 6.8 Hz, 1 H), 4.94 (d, $J = 16.8$ Hz, 1 H), 4.56 (d, $J = 16.8$ Hz, 1 H), 4.16 (br. s, 1 H), 2.66 - 2.50 (m, 2 H), 2.04 - 1.95 (m, 1 H), 1.91 - 1.84 (m, 1 H), 1.55 (s, 9 H);

**$^{13}$C NMR (101 MHz, CDCl$_3$):** $\delta$ 155.4, 137.8, 131.7, 130.5, 130.2, 128.5, 126.9, 126.7, 126.5, 126.4, 126.0, 80.7, 57.2, 45.6, 34.3, 30.0, 28.5;

**HRMS-ESI(m/z):** calcd. for C$_{23}$H$_{28}$N$_2$NaO$_2$ [M+Na]$^+$ 387.2048, found 387.2050.
3-\((\text{tert}-\text{butyl})\) 1-ethyl 1,4-dihydrophthalazine-1,3(2\(H\))-dicarboxylate (308): Following one-pot procedure \(A\), reaction was run on 0.40 mmol scale for 1h and compound 308 (109 mg) was obtained in 89% yield after purification by flash chromatography (0% to 3% MeOH in DCM).

**IR (film):** 3291, 3066, 2979, 2932, 1729, 1692, 1478, 1453, 1386, 1367, 1234, 1162, 1126, 1024, 749 cm\(^{-1}\);

**\(^1\)H NMR** (300 MHz, CDCl\(_3\)): \(\delta\) 7.36 - 7.22 (m, 3 H), 7.16 (d, \(J = 7.3\) Hz, 1 H), 4.81 (s, 1 H), 4.74 (d, \(J = 16.5\) Hz, 1 H), 4.65 (d, \(J = 16.5\) Hz, 1 H), 4.25 (q, \(J = 7.2\) Hz, 2 H), 1.52 (s, 9 H), 1.32 (t, \(J = 7.2\) Hz, 3 H);

**\(^{13}\)C NMR** (75 MHz, CDCl\(_3\)): \(\delta\) 170.5, 154.6, 132.2, 130.5, 127.7, 127.2, 126.6, 126.4, 81.1, 61.7, 59.8, 46.0, 28.4, 14.1;

**HRMS-EI(m/z):** calcd. for C\(_{16}\)H\(_{22}\)N\(_2\)NaO\(_4\)[M+Na]\(^+\) 329.1477, found 329.1475.

\[\text{308}\]

**tert-butyl 6-fluoro-4-phenyl-3,4-dihydrophthalazine-2(1\(H\))-carboxylate (309):** Following cyclization procedure \(B\), the reaction of hydrazone 330 was run on 0.30 mmol scale for 1.5h and compound 309 (86 mg) was obtained in 91% yield after purification by flash chromatography (3% to 20% EtOAc in hexanes).
IR (film): 3358, 3063, 2935, 1681, 1447, 1369, 1250, 1146, 1113, 892, 760, 701 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): δ 7.40 - 7.32 (m, 3 H), 7.30 - 7.27 (m, 2 H), 7.16 (dd, J = 8.5, 5.4 Hz, 1 H), 6.96 (td, J = 8.5, 2.5 Hz, 1 H), 6.56 (dd, J = 9.5, 2.5 Hz, 1 H), 5.21 (s, 1 H), 4.80 (s, 2 H), 1.41 (s, 9 H);

¹³C NMR (75 MHz, CDCl₃): δ 162.9, 159.6, 154.5, 139.9, 129.3, 128.9, 128.6, 128.3, 128.1, 128.1, 127.4, 127.3, 114.7, 114.4, 114.1, 81.2, 61.9 61.8, 45.8, 28.3;

HRMS-ESI(m/z): calcd. for C₁₉H₂₁FN₂NaO₂ [M]+ 351.1485, found 351.1489.

**tert-butyl 7-methoxy-4-phenyl-3,4-dihydropthalazine-2(1H)-carboxylate (310):** Following cyclization procedure B, the reaction of hydrazone 333 was run on 0.30 mmol scale for 1.5h and compound 310 (97 mg) was obtained in 95% yield after purification by flash chromatography (3% to 25% EtOAc in hexanes).

IR (film): 3298, 3063, 3000, 2978, 2929, 2858, 1669, 1484, 1454, 1384, 1367, 1238, 1167, 1118, 801, 749, 698 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.33 - 7.30 (m, 5 H), 6.79 - 6.70 (m, 3 H), 5.19 (s, 1 H), 4.81 (br. s, 3 H), 3.82 (s, 3 H) 1.41 (s, 9 H);

¹³C NMR (101 MHz, CDCl₃): δ 154.6, 149.8, 140.8, 137.2, 129.4, 128.4, 127.9, 126.7, 124.3, 115.0, 80.7, 66.8, 62.2, 49.4, 45.6, 28.3;

**tert-butyl 6-morpholo-4-phenyl-3,4-dihydrophthalazine-2(1H)-carboxylate (311):**

Following cyclization procedure B, the reaction of 338 was run on 0.143 mmol scale for 1.5h and compound 311 (55 mg) was obtained in 97% yield after purification by flash chromatography (5% to 60% EtOAc in hexanes).

**IR (film):** 3283, 3061, 2965, 2925, 2855, 1689, 1508, 1451, 1382, 1368, 1236, 1167, 1122, 869, 757, 701 cm⁻¹;

**¹H NMR (400 MHz, CDCl₃):** δ 7.35 - 7.27 (m, 5 H), 7.11 (d, J = 8.3 Hz, 1 H), 6.86 (dd, J = 8.3, 2.1 Hz, 1 H), 6.41 (s, 1 H), 5.16 (s, 1 H), 4.79 (d, J = 15.5 Hz, 1 H), 4.68 (d, J = 15.5 Hz, 1 H), 3.80 (t, J = 4.7 Hz, 4 H), 3.05 - 2.98 (m, 4 H) 1.36 (s, 9 H);

**¹³C NMR (101 MHz, CDCl₃):** δ 154.6, 149.8, 140.8, 137.2, 129.4, 128.4, 127.9, 126.7, 124.3, 115.0, 80.7, 66.8, 62.2, 49.4, 45.6, 28.3;

**HRMS-ESI(m/z):** calcd. for C₂₃H₃₀N₅O₃ [M+H]⁺ 396.2287, found 396.2286.

**tert-butyl-1-methyl-4-phenyl-3,4-dihydrophthalazine-2(1H)-carboxylate (313):** Following cyclization procedure B, reaction was run on 0.25 mmol scale for 30 min with methanol as the solvent instead of toluene. Compound 313 (65 mg) was obtained in 80% yield, as a single
diastereomer, after purification by flash chromatography (3% to 20% EtOAc in hexanes). The relative stereochemistry is confirmed by nOe NMR experiment.

**IR (film):** 3326, 3058, 2990, 2979, 2930, 1666, 1480, 1446, 1390, 1366, 1247, 1169, 1130, 759, 699 cm⁻¹;

**¹H NMR** (400 MHz, CDCl₃): δ 7.32 – 7.26 (m, 1 H), 7.26 – 7.21 (m, 3 H), 7.17 (td, J = 7.5, 1.6 Hz, 1 H), 7.09 – 7.05 (m, 2 H), 7.00 (dd, J = 7.5, 1.3 Hz, 1 H), 5.39 – 5.25 (m, 1 H), 5.14 (s, 1 H), 1.55 (d, J = 6.7 Hz, 3 H), 1.15 (s, 9 H);

**¹³C NMR** (101 MHz, CDCl₃): δ 153.6, 142.2, 137.7, 134.6, 129.1, 128.3, 127.5, 127.3, 126.8, 126.6, 80.2, 61.9, 28.1, 21.0;

**HRMS-ESI(m/z):** calcd. for C₂₀H₂₄N₂NaO₂ [M+Na]⁺ 347.1735, found 347.1736.

**tert-butyl-1,4-diphenyl-3,4-dihydropthalazine-2(1H)-carboxylate (316):** Following cyclization procedure B, reaction was run on 0.25 mmol scale for 50 min with methanol as the solvent instead of toluene. Compound 316 (53 mg) was obtained in 55% yield, as a single diastereomer, after purification by flash chromatography (3% to 20% EtOAc in hexanes). The relative stereochemistry is assigned by analogy.

**IR (film):** 3321, 2980, 2925, 2856, 1665, 1474, 1393, 1366, 1317, 1244, 1176, 1125, 759, 700 cm⁻¹;

**¹H NMR** (300 MHz, CDCl₃): δ 7.41 – 7.19 (m, 10 H), 7.18 – 7.05 (m, 4 H), 6.43 (s, 1 H), 5.25 (s, 1 H), 1.14 (s, 9 H);
\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)): \(\delta\) 142.1, 135.3, 134.6, 129.2, 128.9, 128.5, 128.3, 128.2, 127.9, 127.6, 127.2, 127.1, 80.5, 61.7, 29.9, 28.1;

**HRMS-ESI(\(m/z\))**: calcd. for C\(_{25}\)H\(_{26}\)N\(_2\)NaO\(_2\) [M+Na]\(^+\) 409.1892, found 409.1888.
Chapter 5: Applications of Radical Cyclization
Approaches to the Syntheses of Nitrogen-Containing Moieties

In Chapter 4, a new method using 6-endo-trig radical cyclization onto hydrazones was introduced for the regiocontrolled and stereoselective syntheses of tetrahydrophthalazines. Considering the efficiency and robustness of this method, we hypothesized that this radical cyclization approach may be applied to the syntheses of other important nitrogen heterocycles, such as azaphthalazine and pyridazine derivatives (Figure 5.1), both of which are important heterocyclic motifs used in pharmaceutically relevant molecules.283-287

![Figure 5.1](image)

Figure 5.1. Radical cyclization approaches to other nitrogen-containing motifs.

Synthetic approaches to reduced phthalazine derivatives generally involve the reduction of phthalazinones or phthalazines to access to form the corresponding di- and tetrahydrophthalazines.237-239,241 These reductive processes typically display poor regio- or stereochemical control. Hence, we surmised that our radical cyclization method can selectively
access dihydro- and aromatic phthalazines from tetrahydrophthalazines through oxidative processes.

Tetrahydrophthalazines can also be versatile intermediates for other nitrogen-containing moieties. The substituted tetrahydrophthalazines that can be synthesized by our new radical cyclization methodology contain the core structures of various phthalazine-based drug analogs, such as pyrazolo phthalazine-based drug analog 214 (Figure 4.3). In addition, we conceived that tetrahydrophthalazines could be useful precursors for the regio- and stereoselective syntheses of 1,4-diamines through reductive N-N bond cleavage.288-291

5.1 Syntheses of tetrahydro-azaphthalazines and -pyridazines

Azaphthalazine and pyridazine derivatives have been applied as nitrogen heterocycles in drug analogs with diverse bioactivities.283-287 The syntheses of azaphthalazines and pyridazines follow a similar approach as that to phthalazine: condensation of diketone or dicarboxylic acid anhydride with hydrazine (Figure 4.5).292 However, the limitations of this approach in regio- and stereoselectivity hinders the exploration of the corresponding saturated or partially saturated ring systems, such as tetrahydro-azaphthalazines and -pyridazines. With the development of 6-endo-trig radical cyclization of hydrazones, we hypothesized that a radical cyclization could be a potential method to regio- and stereoselectively access tetrahydro-azaphthalazines and -pyridazines.

5.1.1 6-Endo-trig radical cyclization to access tetrahydroazaphthalazines

To explore the radical cyclization approach to tetrahydroazaphthalazines, 2-bromopyridine-tethered aryl hydrazone 350 was synthesized by following the synthetic route 2 (Scheme 4.22), and subsequently subjected to the conditions with Et3B and TTMSS under nitrogen atmosphere (Table 5.1, Entry 1). 1H NMR spectroscopic analysis of the reaction mixture showed that the
desired cyclized product \(351\) was indeed obtained, but as a minor product, while the major product was the dehalogenated hydrazone \(352\). Compared to the results we had obtained with \(N-(o\text{-bromobenzyl})\) hydrazones (Chapter 4), this result suggested that the radical cyclization of a 2-pyridyl radical is slower than that of a phenyl radical, and unable to compete against the intermolecular HAT process. Additions of TTMSS and \(\text{Et}_3\text{B}\) to the reaction mixture at slower rates increased the product ratios to 1.4 : 1 in favor of the cyclized product (Table 5.1, Entry 2 and 3).

The cyclization of \(350\) was also tested under air atmosphere with toluene that was not specially dried. However, it did not have a beneficial effect on the product ratio (Table 5.1, Entry 4) compared to that under nitrogen atmosphere and anhydrous conditions. Several protic solvents were then tested for the synthesis of tetrahydroazaphthalazine \(351\), including MeOH, trifluoroethanol (TFE), and hexafluoroisopropanol (HFIP). The results showed that the product ratios increased in the order of MeOH, TFE, and HFIP, in favor of the cyclized product (Table 5.1, Entry 5, 6, and 7). The increased preference for cyclization may be attributed to the increasing acidity and polarity of the solvents. The use of HFIP as the solvent afforded tetrahydroazaphthalazine \(351\) as the major product with almost no formation of dehalogenated product \(352\) (Table 5.1, Entry 7). However, only moderate conversions were obtained in the reactions using TFE and HFIP. The decreased conversions are likely due to the reactions between the acidic protic solvents and TTMSS, which was evidenced by the observation of gas evolution after the addition the TTMSS.\(^{293}\) This problem was addressed by increasing the amount of TTMSS; the reaction with five equivalents of TTMSS was able to achieve full conversion in 10 minutes with 17:1 product ratio, and afforded product \(351\) in 83% isolated yield.
Table 5.1. Optimization on the radical cyclization of 350 to synthesize tetrahydroazaphthalazine 351.

<table>
<thead>
<tr>
<th>Entry</th>
<th>x</th>
<th>y</th>
<th>Solvent</th>
<th>Atm.</th>
<th>T(°C)</th>
<th>Conversion(%)</th>
<th>Ratio(351:352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td>2.5</td>
<td>10</td>
<td>toluene</td>
<td>N₂</td>
<td>50</td>
<td>&gt;95</td>
<td>0.1:1</td>
</tr>
<tr>
<td>2[a]</td>
<td>2.5</td>
<td>10</td>
<td>toluene</td>
<td>N₂</td>
<td>50</td>
<td>&gt;95</td>
<td>0.8:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(over 2 h)</td>
<td></td>
</tr>
<tr>
<td>3[a]</td>
<td>2.5</td>
<td>10</td>
<td>toluene</td>
<td>N₂</td>
<td>50</td>
<td>&gt;95</td>
<td>1.4:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(over 12 h)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>5</td>
<td>toluene</td>
<td>air</td>
<td>rt</td>
<td>&gt;95</td>
<td>0.1:1</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>5</td>
<td>MeOH</td>
<td>air</td>
<td>rt</td>
<td>&gt;95</td>
<td>1.8:1</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>5</td>
<td>TFE</td>
<td>air</td>
<td>rt</td>
<td>44</td>
<td>5.6:1</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>5</td>
<td>HFIP</td>
<td>air</td>
<td>rt</td>
<td>45</td>
<td>14:1</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>5</td>
<td>HFIP</td>
<td>air</td>
<td>rt</td>
<td>&gt;95</td>
<td>17:1 (83%)[b]</td>
</tr>
</tbody>
</table>

All the reactions were run on 0.1 mmol scale and analyzed by ¹H NMR spectroscopy to determine the conversions and product ratios. [a] Reactions were run under anhydrous conditions with dry solvents. [b] Isolated yield of 351.

5.1.2 6-Endo-trig radical cyclization to access tetrahydropyridazines

It has been shown by my colleague, Dr. Natalie Campbell, in a previous study that N-(3-bromoallyl) aryl hydrazones did not undergo radical cyclization when AIBN and Bu₃SnH were used. From the wide scope displayed in our studies of radical cyclizations utilizing the triethylborane/O₂ system (Scheme 4.24), we hypothesized that N-(3-bromoallyl) aryl hydrazones...
may be tolerated in our new radical cyclization method. To explore this hypothesis, 3-bromoallyl hydrazone 353 was prepared following the route 2 (Scheme 4.22), and was then subjected to the standard conditions under air atmosphere. Gratifyingly, it was observed that the reaction afforded 80% conversion of the starting material to the desired cyclized product. Further optimizations showed that an increase in the amount of TTMSS to four and half equivalents led to a full conversion and afforded tetrahydropyridazine 354 in 82% isolated yield (Scheme 5.1, 1). Under the same reaction conditions, substituted N-(3-bromoallyl) hydrazone 355 was also able to afford the corresponding tetrahydropyridazine 356 in 89% isolated yield (Scheme 5.1, 2). Both reactions showed no obvious side-products, and the alkene moieties were left intact.

![Scheme 5.1](image)

**Scheme 5.1.** Radical cyclization of alkene-tethered hydrazones to synthesize substituted tetrahydropyridazines.

### 5.2 Syntheses of diverse phthalazine derivatives from tetrahydrophthalazines

#### 5.2.1 Syntheses of dihydro- and aromatic phthalazines from tetrahydrophthalazines

We envisaged that our radical cyclization protocols could provide alternative approaches for the syntheses of dihydro- and aromatic phthalazines from tetrahydrophthalazines, which have the potential to address the challenges of regio- and stereoselectivities (Scheme 5.2). Since the tetrahydrophthalazine products from our 6-endotr radical cyclizations have one of the nitrogen
atoms protected by use of a Boc group, we proposed that dihydrophthalazines can be effectively accessed through selective oxidations of the tetrahydrophthalazines. Oxidations of amines to imines have been achieved in different reported methods.\textsuperscript{294,295} These methods generally follow the strategy of functionalizing the nitrogen atoms with good leaving groups before $\beta$-elimination to form the C=N bonds. In the case of Boc-protected tetrahydrophthalazines, we proposed that the N-H bond can be easily converted to an N-Halogen bond, which would further undergo $\beta$-elimination under basic conditions.

![Scheme 5.2](image)

**Scheme 5.2.** Radical cyclization and oxidation to access high oxidation-state phthalazines from hydrazones.

To test whether our tetrahydrophthalazine products could be converted to the corresponding dihydrophthalazines, Boc-protected tetrahydrophthalazine 287 was subjected to anhydrous conditions with sodium hydride before the treatment with $N$-chlorosuccinimide (NCS) to form an N-Cl bond. After full conversion, potassium tert-butoxide was added to effect $\beta$-elimination (Scheme 5.3, 1). $^1$H NMR spectroscopic analysis showed that the reaction resulted in good conversion to dihydrophthalazine 357, although 34% of the starting material remained. Based on the analysis by MS during the course of sequential reaction, it was observed that some dihydrophthalazine 357 had formed prior to the addition of potassium tert-butoxide. It was proposed that the succinimidate formed from NCS could serve as the base in $\beta$-elimination step. Therefore, the reaction was tested with five equivalents of NaH and two and a half equivalents of
NCS, but without any external base. The reaction achieved full conversion, and gave the dihydrophthalazine 357 in 72% isolated yield (Scheme 5.3, 2).

![Scheme 5.3. Selective oxidation of tetrahydrophthalazine 287 to form dihydrophthalazine 357.](image)

We next explored the direct oxidation of tetrahydrophthalazines to aromatic phthalazines using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Because DDQ is a strong oxidant, we hypothesized that it may be able to directly deprotect and oxidize the Boc-protected tetrahydrophthalazines in a one-pot process. Therefore, 287 was subjected to an excess amount of DDQ in anhydrous benzene at room temperature, but a complex mixture of multiple products was obtained, including dihydrophthalazine 357.

The tetrahydrophthalazine trifluoroacetic acid salt, obtained via Boc-deprotection, was then subjected to the oxidative conditions with DDQ. However, the phthalazine product was not obtained based on NMR spectroscopic analysis. When tetrahydrophthalazine hydrogen chloride salt was prepared, and then treated with DDQ, the aromatic phthalazine 358 was obtained in quantitative yield over two steps (Scheme 5.4).
Scheme 5.4. Oxidation of tetrahydrophthalazine 287 by DDQ to form aromatic phthalazine 358.

5.2.2 Syntheses of pyrazolo phthalazine dione derivatives

Multi-substituted tetrahydrophthalazines have been used as important frameworks in various drug analogs, such as central nerve system depressants, and antihypertensive drug analogs (Figure 4.3). Considering the issues in traditional approaches to their syntheses (Chapter 4, Section 4.2), we applied our radical cyclization protocols to the syntheses of the relevant pharmaceutical analogs or intermediates.

We began with an effort toward the synthesis of bioactive analog 214. It was proposed that these fused pyrazolo phthalazines can be readily synthesized from the corresponding diones by reduction (Figure 5.2). These pyrazolo phthalazine diones can be formed by the diacylation of tetrahydrophthalazine, which are easily accessible from our new cyclization methodology.

Figure 5.2. Retrosynthetic analysis of tricyclic bioactive analogs with tetrahydrophthalazine moiety.

The Boc-protected tetrahydrophthalazine 292 was synthesized in 85% yield through our one-pot protocol using a radical cyclization directly from 4-chlorobenzaldehyde and Boc-hydrazone (Scheme 5.5, 1). After deprotection by hydrochloric acid, the tetrahydrophthalazine hydrogen chloride salt was subjected to the anhydrous conditions with 4-(N-dimethylamino)pyridine (DMAP) as a base before reacting with malonyl dichloride to afford the
dione 359 in 45% yield over two steps. To demonstrate the accessibility of different substitutions of the analogs, we next examined unsymmetric substitution on the tetrahydrophthalazine core. 6-Methoxy substituted tetrahydrophthalazine 310 was readily obtained in 85% yield over two steps using route 2 of the radical cyclization protocols (Scheme 5.5, 2). Following the same procedures as that of 359, 6-methoxy pyrazolo phthalazine dione 360 was synthesized in 66% yield over two steps.

Scheme 5.5. Syntheses of pyrazolo phthalazine dione derivatives through the radical cyclization of hydrazones.

The conversion of diones 359 and 360, to the pyrazole phthalazine drug analogs was tested with the reduction by lithium aluminum hydride (LAH).237,239 Preliminary results showed that the reduction afforded full conversion to the desired analogs based on the MS analysis of the reaction mixtures. In all, these results demonstrated the feasibility and efficiency of radical cyclizations of hydrazones for the syntheses of phthalazine-based pharmaceutical analogs, especially for the exploration of new structural features that are challenging for traditional methods.
5.3 Syntheses of 1,4-diamines from tetrahydrophthalazines

Diamines are important motifs not only as ligands in organometallics, but also as common building blocks in pharmaceutical syntheses. A large variety of methods have been developed for the regio- and stereoselective syntheses of diamines, especially 1,2- and 1,3-diamines. However, there have not been many methods that can be used to efficiently access 1,4-diamines. The strategies reported in literature generally make use of substitution reactions of corresponding alcohols, Mannich-type reaction, or diaza-[4+2] reactions between dienes or naphthalene derivatives and diazo compounds, such as dialkyl azodicarboxylate, and 1,2,4-triazoline-3,5-dione. The resultant cyclic hydrazines can be converted to 1,4-diamines after N-N bond cleavage. Nonetheless, it is challenging for these strategies to achieve asymmetrical syntheses of 1,4-diamines.

Cyclic hydrazines, such as phthalazine and pyridazine derivatives, have been conceived as potential synthons for 1,4-diamines. Based on our studies of radical cyclizations (see Chapter 4), we believed that the 6-endo-trig radical cyclization of hydrazones would provide a potential solution to selectively synthesize 1,4-diamines through tetrahydrophthalazine intermediates.

5.3.1 Exploration on the cleavage of N-N bonds of tetrahydrophthalazines

A number of different conditions have been reported for the cleavage of N-N bonds, using either reductive conditions, such as Raney-Ni, Pd/C, TiCl₃, PtO₂, Zn powder and BH₃, or oxidative conditions, such as magnesium monoperoxyphthalate (MMPP) hexahydrate and m-CPBA. The oxidative methods with peroxides involve the formation of hydrazide N-oxide intermediates, and form amines and nitrones after N-N bond cleavage, which
would be destructive to the adjacent C$_{sp^3}$ structures. The reductive methods, except for those using PtO$_2$, Raney-Ni and TiCl$_3$, usually require specific functional groups on the nitrogen of cyclic hydrazines, such as acyl, allyloxy carbonyl (Alloc) and carboxybenzyl (Cbz).

Reduction using H$_2$/Raney-Ni has shown good versatility for the cleavage of N-N bonds in diverse substrates. It has been reported that Raney-Ni mediated hydrogenation was able to cleave the N-N bond of cyclic hydrazine 361 with no functional groups on the nitrogen atoms (Scheme 5.6, 1). However, better efficiency was usually seen for the N-N bond cleavage when the hydrazine nitrogen atoms are substituted with carbonyl based functional groups, such as acyl and Cbz group (For an example, see Scheme 5.6, 2). TiCl$_3$ and H$_2$/PtO$_2$ conditions were less dependent on the functional groups on the nitrogen atoms of hydrazines/hydrazides in the cleavage of N-N bonds (Scheme 5.6, 3 and 4).

Scheme 5.6. Representative examples of N-N cleavage using Raney-Ni, TiCl$_3$, or PtO$_2$. 

\[ \text{Ph,} \quad \text{H} \quad \text{N} \quad \text{NH} \quad \text{Ph} \quad \text{H}_2, \text{Raney-Ni} \quad \text{ultrasound} \quad \text{Ph,} \quad \text{H} \quad \text{N} \quad \text{NH} \quad \text{Ph} \quad \text{362} \quad 74\% \]

\[ \text{HN}^\text{=O} \quad \text{Ph} \quad \text{363} \quad \text{Raney-Ni} \quad \text{H}_2 \text{(balloon)} \quad \text{EtOH, 80 °C} \quad \text{NH}_2 \quad \text{O} \quad \text{Ph} \quad \text{NH} \quad \text{NH} \quad \text{2} \quad 94\% \]

\[ \text{R} \quad \text{H} \quad \text{N} \quad \text{NH}_2 \quad \text{4 equiv aq. TiCl}_3 \quad \text{or} \quad \text{cat. TiCl}_4, \text{Mg} \quad \text{NH}_2 \quad \text{+} \quad \text{NH}_3 \quad \text{>90\%} \]

\[ \text{HOOC} \quad \text{78} \quad \text{COOH} \quad \text{NH} \quad \text{NH} \quad \text{H}_2, \text{PtO}_2 \quad \text{4 atm H}_2 \quad \text{2 N HCl} \quad \text{HOOC} \quad \text{78} \quad \text{COOH} \quad \text{NH}_2 \quad \text{NH}_2 \quad \text{92-97\%} \]

n = 1, 2, 3
To explore the conditions for the N-N bond cleavage of tetrahydrophthalazines, tetrahydrophthalazines 365 and 301, were treated with Zn in AcOH or TFA. However, both proved ineffective for Boc-protected or nonprotected tetrahydrophthalazines, and no conversion of the starting material was observed (Scheme 5.7, 1). We next tested Raney-Ni conditions. At first, we subjected Boc-protected tetrahydrophthalazine 301 to an excess of Raney-Ni in methanol under thermal conditions, which aimed to make use of the reductive ability of Raney-Ni itself. However, no conversion to the diamines 366 or 367 was observed (Scheme 5.7, 2). When the tetrahydrophthalazine hydrogen chloride salt 365 was subjected to an excess Raney-Ni under a balloon of hydrogen, approximately a 1:1 ratio mixture of tetrahydrophthalazine and diamine was observed as well as many unidentified side products (Scheme 5.7, 3). Further increasing the reaction time did not improve the formation of diamine 366, but resulted in the decomposition of 366. We hypothesized that possible undesired side reactions that may be competing with the
cleavage of N-N bonds are the oxidation of hydrazine, and the deamidation through the cleavage of C-N bonds under the hydrogenation conditions (Figure 5.3).

![Diagram of hydrogenation processes involving tetrahydrophthalazines]

**Figure 5.3.** Possible processes in the transition metal-catalyzed hydrogenation of tetrahydrophthalazines.

We hypothesized that more powerful and efficient hydrogenating reagents may be required to selectively convert tetrahydrophthalazines to the corresponding diamines. Therefore, PtO$_2$/H$_2$ was examined for the hydrogenative N-N bond cleavage of Boc-protected tetrahydrophthalazine 287. Following a procedure reported in literature, 287 was subjected to an aqueous hydrochloric acid solution with PtO$_2$ catalyst under a hydrogen atmosphere (Scheme 5.8, 1). It was observed that only the deprotected tetrahydrophthalazine 368 was formed with no further conversion to diamine. However, when the tetrahydrophthalazine hydrogen chloride salt 365 was prepared separately from the corresponding Boc-protected tetrahydrophthalazine 301, and then subjected to the conditions with PtO$_2$ in methanol under a hydrogen atmosphere, the reaction proceeded to full conversion after 24 h, the desired diamine 366 as the major product (Scheme 5.8, 2). The MS analysis of reaction mixture showed that several side products were formed in the reaction, and one of side products was postulated to be 370 which may be produced through deamination. In
order to isolate the desired product, the diamine 366 was subsequently Boc-protected to afford 369 in 49% yield over three steps from the Boc-protected tetrahydrophthalazine 301.

![Scheme 5.8. Exploration of N-N bond cleavage by PtO₂/H₂ system.](image)

To test the aryl substituted tetrahydrophthalazines for the syntheses of 1,4-diamines using lower catalyst loadings, 1-phenyl tetrahydrophthalazine hydrogen chloride salt 368 was subjected to 12 mol% PtO₂ in methanol under 5 bar of hydrogen. Unfortunately, no diamine was observed after an overnight reaction (Scheme 5.9, 1). Higher pressures of hydrogen, such as 25 and 50 bar, were examined, but the reactions were still unable to achieve high conversion. Side products were always observed in these experiments, the major of which was proposed to be deaminated product, 1-phenylisoindoline, based on MS analysis.

After optimizing the catalyst loadings and the hydrogen pressures, the N-N bond cleavage of 368 achieved full conversion using 25 mol% PtO₂ and 25 bar hydrogen atmosphere. Side products were still observed, including 1-phenylisoindoline. After protection of the diamine by Boc₂O in one-pot, 372 was obtained in 69% yield overall (Scheme 5.9, 2).
Scheme 5.9. Exploration of N-N bond cleavage of \( \text{368} \) under high pressure of hydrogen gas with a low catalyst loading.

Next, a one-pot procedure to access diamines from hydrazones was also investigated (Scheme 5.10). Hydrazone \( \text{286} \) was subjected to radical cyclization conditions, and was then concentrated \textit{in vacuo} to afford the crude Boc-tetrahydrophthalazine product \( \text{287} \). Deprotection of the crude \( \text{287} \) using hydrochloric acid followed by PtO\(_2\)-catalyzed hydrogenation afforded the crude 1,4-diamine \( \text{371} \). A final protection with Boc\(_2\)O afforded the protected diamine \( \text{372} \) in 56% yield over four steps.

Scheme 5.10. One-pot procedure to access Boc-protected 1,4-diamine \( \text{372} \) from hydrazone \( \text{286} \).

5.3.2 Syntheses of diamines from Boc-protected tetrahydrophthalazines

With the optimized conditions for N-N bond cleavage, we next investigated tetrahydrophthalazines with different substituents for the syntheses of diamines. The preliminary
results demonstrated that different functional groups, such as fluorine (291 and 309), \textit{tert}-butyl (290), or methoxyl (310), on either the phenyl substituent or the phthalazine ring of Boc-tetrahydrophthalazines can be tolerated in the syntheses of Boc-protected diamines (Scheme 5.11). The PtO\textsubscript{2}-catalyzed hydrogenation step generally required prolonged reaction times for good yields, even under high pressure hydrogen atmosphere.

![Scheme 5.11](image)

**Scheme 5.11.** One-pot procedure for the syntheses of diamines from substituted tetrahydrophthalazines via Pt-catalyzed hydrogenation.

### 5.4 Conclusions

We have applied \textit{6-endo-trig} radical cyclization to the syntheses of tetrahydroazaphthalazines and \textit{pyridazines}. Moreover, we have developed new approaches to access high oxidation-state phthalazine derivatives from substituted tetrahydrophthalazines synthesized using our radical
cyclization conditions. These approaches could potentially address the issues of regio- and stereoselectivity in the syntheses of dihydro- and aromatic phthalazines.

To demonstrate the practical utility of 6-endo-trig radical cyclization of hydrazones, we conducted the studies toward the syntheses of pharmaceutical analogs and accessed two pyrazolo phthalazine diones, which can be useful intermediates to prepare tricyclic tetrahydro-pyrazolo phthalazines. We also showed that the radical cyclization of hydrazones can offer the opportunity to explore new chemical space that is difficult to access using traditional methodologies.

At last, we successfully developed a PtO$_2$-catalyzed hydrogenation method for the N-N bond cleavage of substituted tetrahydrophthalazines as a new route to access 1,4-diamines. We have also demonstrated that the key radical cyclization and hydrogenation can be combined in an one-pot process to directly convert a prefunctionalized hydrazones to a Boc-protected diamines. Preliminary studies have shown that Boc-protected 1,4-diamines with different substituents can be synthesized from the corresponding Boc-tetrahydrophthalazines through the PtO$_2$-catalyzed hydrogenation in moderate to good yields.

5.5 Experimental information

General methods and instrumentation

Reagents and solvents were purchased from commercial sources and used as received, unless otherwise stated. Triethylborane (Et$_3$B) reagent was purchased as a 1.0 M solution in hexanes under inert atmosphere. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM) and N,N-dimethylformamide (DMF) were obtained by first sparging nitrogen gas through the solvents for one hour and then passing the solvents through activated alumina columns. Yields refer to
chromatographically and spectroscopically homogeneous material, unless otherwise stated. The solid phase in the flash chromatography purification was Silicycle F60 silica gel (230–400 mesh).

A KD–Scientific KDS100 syringe pump was used for all slow additions. Infrared spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer. Nuclear magnetic resonance spectra were recorded using a Bruker AV-300 or 400 spectrometers. Low and high-resolution mass spectra were recorded on either a Bruker Esquire-LC spectrometer (LRMS) or a Waters/Micromass LCT spectrometer (for HRMS).

**Syntheses of hydrazones**

![Chemical diagram]

**tert-butyl 2-benzylidene-1-((2-bromopyridin-3-yl)methyl)hydrazine-1-carboxylate (350)**: To a solution of 2-bromonicotinaldehyde (377, 1.00 g, 5.38 mmol) in methanol (13.4 mL) was added NaBH₄ in one portion at room temperature. Vigorous bubbling was observed and the reaction was stirred for 2 h before being diluted with EtOAc (40 mL). The mixture was then washed with saturated aq. NH₄Cl solution (50 mL) and brine (40 mL x 2), dried over sodium sulfate and concentrated in vacuo to afford the alcohol product as a liquid (1.01 g) in quantitative yield. The alcohol product (424 mg, 2.23 mmol) was then dissolved in DCM (12.4 mL) and to the reacting solution was added PBr₃ (0.42 mL, 4.46 mmol) in one portion at room temperature. The mixture was stirred at 42 °C for overnight. After dilution with saturated aq. NaHCO₃ (30 mL) and water (20 mL), the mixture was extracted with EtOAc (30 mL x 3). The combined organic layer was
washed with brine (30 mL x 2), dried over sodium sulfate and concentrated in vacuo to afford 378 as a clear liquid (603 mg) in quantitative yield, which was used directly for next step.

Following the procedure for the synthesis of hydrazone 286, hydrazone 350 was afforded from 378 in 57% yield as a white solid (500 mg) after purification via silica gel-based flash chromatography (2% to 16% EtOAc in hexanes).

**IR (neat):** 3061, 2978, 2933, 1734, 1703, 1561, 1404, 1368, 1343, 1286, 1244, 1151, 1117, 1052, 895, 757, 694 cm\(^{-1}\);

**\(^1\)H NMR (300 MHz, CDCl\(_3\)):** \(\delta 8.32 (dd, J = 4.7, 1.9 \text{ Hz}, 1 \text{ H}), 7.69 - 7.62 (m, 2 \text{ H}), 7.58 (br. s, 1 \text{ H}), 7.40 - 7.34 (m, 4 \text{ H}), 7.25 (dd, J = 7.7, 4.7 \text{ Hz}, 1 \text{ H}), 5.17 (s, 2 \text{ H}), 1.61 (s, 9 \text{ H});

**\(^{13}\)C NMR (75 MHz, CDCl\(_3\)):** \(\delta 153.5, 149.1, 142.0, 136.1, 136.0, 134.7, 132.4, 129.9, 128.8, 127.4, 123.4, 82.8, 47.9, 28.4;

**HRMS-ESI(m/z):** calcd. for C\(_{18}\)H\(_{20}\)Br\(_3\)NaO\(_2\) [M+Na]\(^+\) 412.0635, found 412.0637.

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**tert-butyl 2-benzylidene-1-(3-bromo-2-methylallyl)hydrazine-1-carboxylate (353):** To a mixture of Boc-hydrazone (326, 330 mg, 1.5 mmol) and tetrabutylammonium iodide (TBAI, 55 mg, 0.15 mmol) in anhydrous THF (6 mL) was added sodium hydride (90 mg, 1.5 equiv, 60% dispersion in mineral oil) in one portion. Once the gas evolution ceased, the reaction mixture was warmed up to 40 °C and a 1.0 M solution of 1,3-dibromo-2-methylprop-1-ene (379, 401 mg, 1.88 mmol) in anhydrous THF was added dropwise. After the reaction was stirred at 40 °C for overnight, it was cooled down to room temperature and quenched by the addition of a saturated
aq. NaHCO₃ solution (3 mL). After dilution with water (2 mL) and brine (10 mL), the mixture was extracted with EtOAc (10 mL). The organic phase was washed with brine (20 mL x 2), dried over sodium sulfate and concentrated in vacuo to get crude mixture which was purified via silica gel-based flash chromatography (0% to 15% ether in hexanes) to afford alkylated hydrazone 353 (351 mg) in 66% yield as a white solid.

**IR (neat):** 3026, 2978, 2929, 2869, 2852, 1700, 1450, 1407, 1393, 1367, 1334, 1288, 1228, 1148, 755, 693 cm⁻¹;

**¹H NMR (300 MHz, CDCl₃):** δ 7.73 (br. s, 1 H), 7.70 - 7.63 (m, 2 H), 7.41 - 7.30 (m, 3 H), 6.02 (d, J = 1.4 Hz, 1 H), 4.48 (s, 2 H), 1.83 (s, 3 H), 1.57 (s, 9 H);

**¹³C NMR (75 MHz, CDCl₃):** δ 153.2, 141.6, 135.7, 134.9, 129.6, 128.6, 127.2, 103.7, 82.2, 50.6, 28.3, 17.3;

**HRMS-ESI(m/z):** calcd. for C₁₆H₂₁BrN₂O₂ [M+Na]⁺ 375.0676, found 375.0684.

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3-bromo-2-methylbut-2-en-1-ol (382): To a solution of acid 380 (2.00 g, 20 mmol) in chloroform (2 mL) was added a solution of Br₂ (20 mmol) in chloroform (2 mL) dropwise over 45 min at room temperature. After stirring for 3 h, the mixture was quenched with saturated aq. NaHSO₃ solution (5 mL) and diluted with chloroform (2 mL). The organic layer was washed with water (5 mL x 2), dried over sodium sulfate and concentrated in vacuo to get crude mixture. The crude mixture was treated with aq. solution of NaOH (3.60 g, 90 mmol) in water (10 mL). The mixture was then stirred at room temperature for 2 days, before acidified by aq. 5.4 M HCl solution.
till the pH reached 1~2. The mixture was then extracted with diethyl ether (50 mL x 2), and the combined organic layers were dried over sodium sulfate, and concentrated in vacuo to afford the acid **381** as a white solid (1.32 g) in 37% yield.

This acid **381** was then dissolved in anhydrous THF (15 mL) and was added LAH (560 mg, 14.74 mmol, 2 equiv) in several portions at 0 °C. The reaction was allowed to warm up to room temperature gradually and stirred overnight. Then the reaction was quenched with saturated aq. NaHCO₃ (30 mL) and extracted with diethyl ether (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate and concentrated in vacuo to obtain the alcohol **382** as a clear liquid (539 mg) in 44% yield for direct use without further purification.

The NMR data of the product match the literature value.³⁸

**¹H NMR (300 MHz, CDCl₃):** δ 7.57 (dd, J = 7.8, 1.1 Hz, 1 H), 7.37 - 7.29 (m, 1 H), 7.24 - 7.11 (m, 2 H), 4.70 (s, 2 H), 4.09 (br. s, 2 H), 1.49 (s, 9 H);

**¹³C NMR (75 MHz, CDCl₃):** δ 156.9, 137.0, 132.9, 128.6, 128.5, 127.4, 123.1, 81.1, 54.6, 28.4.

**tert-butyl 2-benzylidene-1-(3-bromo-2-methylbut-2-en-1-yl)hydrazine-1-carboxylate (355):**

Alcohol **383** (182 mg, 1.1 mmol) was dissolved in DCM (6.1 mL) and was added PBr₅ (0.21 mL, 2.2 mmol) in one portion. The reaction was then stirred at 42 °C for overnight. After dilution with saturated aq. NaHCO₃ (6 mL) and water (4 mL), the mixture was extracted with EtOAc (10
mL x 3). The combined organic layers were washed with brine (10 mL x 2), dried over sodium sulfate and concentrated in vacuo to afford product 384 as a clear liquid (228 mg) in 91% yield. Following the procedure for the synthesis of hydrazone 286, hydrazone 355 was afforded from 384 in 57% yield as a white solid (243 mg) after purification via silica gel-based flash chromatography (2% to 10% EtOAc in hexanes).

IR (neat): 3063, 2955, 2925, 2855, 1705, 1450, 1407, 1393, 1348, 1285, 1241, 1154, 755, 693 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): δ 7.78 (br. s, 1 H), 7.69 - 7.63 (m, 2 H), 7.42 - 7.32, (m, 3 H), 4.61 (s, 2 H), 2.48 (s, 3 H), 1.79 (s, 3 H), 1.59 (s, 9 H);

¹³C NMR (75 MHz, CDCl₃): δ 153.5, 142.2, 135.1, 130.3, 129.8, 128.8, 127.3, 118.8, 82.3, 47.3, 28.4, 25.1, 19.9;


**tert-butyl 8-phenyl-7,8-dihydropyrido[2,3-d]pyridazine-6(5H)-carboxylate** (351):

Hydrazone 350 (39 mg, 0.1 mmol) was dissolved in HFIP (5 mL) to form a 0.02 M solution, to which was added (TMS)₃SiH (154 µL, 5 equiv) and a 1.0 M solution of Et₃B (0.50 mL, 5.0 equiv) in hexanes at room temperature. The reaction was stirred for 15 min under air atmosphere at room temperature. Then it was concentrated in vacuo to get crude mixture, which was purified by silica gel-based flash chromatography (0 to 10% MeOH in DCM) to afford 351 (26 mg) in 83% yield.
IR (film): 3270, 3060, 3030, 2977, 2930, 2851, 1689, 1494, 1441, 1388, 1367, 1237, 1164, 1127, 874, 734, 698 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.44 (dd, \(J = 4.9, 1.6\) Hz, 1H), 7.58 – 7.52 (m, 1H), 7.35 – 7.27 (m, 3H), 7.21 (td, \(J = 7.2, 6.0, 3.3\) Hz, 3H), 5.34 (s, 1H), 4.94 (d, \(J = 18.6\) Hz, 1H), 4.71 (d, \(J = 16.5\) Hz, 1H), 1.33 (s, 9H);

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 155.7, 154.6, 148.0, 140.1, 134.3, 129.3, 128.7, 128.6, 128.1, 122.2, 81.3, 64.1, 45.4, 28.3;

HRMS-ESI\((m/z)\): calcd. for C\(_{18}\)H\(_{22}\)N\(_3\)O\(_2\) [M+H]\(^+\) 312.1712, found 312.1711.

tert-butyl 5-methyl-3-phenyl-3,6-dihydropyridazine-1(2\(H\))-carboxylate (354): Hydrazone 353 (110 mg, 0.31 mmol) was dissolved in toluene (15.6 mL) to form a 0.02 M solution, to which was added (TMS)\(_3\)SiH (0.43 mL, 4.5 equiv) and a 1.0 M solution of Et\(_3\)B (1.56 mL, 5.0 equiv) in hexanes at room temperature. The reaction was stirred for 1 h under air atmosphere at room temperature. Then it was concentrated \textit{in vacuo} to get crude mixture, which was purified by silica gel-based flash chromatography (0 to 12\% EtOAc in DCM) to afford 354 (71 mg) in 83% yield.

IR (neat): 3298, 3062, 3028, 2957, 2917, 2850, 1739, 1695, 1467, 1455, 1366, 1382, 1236, 1165, 1119, 757, 700 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.38 - 7.24 (m, 5 H), 5.62 (br. s, 1 H), 4.68 (br. s, 1 H), 4.57 (br. s, 1 H), 3.98 (br. s, 2 H), 1.80 (s, 3 H), 1.39 (s, 9 H);
$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 154.7, 140.6, 132.1, 128.6, 128.4, 127.9, 122.8, 80.7, 58.8, 47.3, 28.4, 20.2;

**HRMS-ESI(m/z):** calcd. for C$_{16}$H$_{22}$N$_2$NaO$_2$ [M+Na]+$^+$ 297.1574, found 297.1579.

**tert-butyl 4,5-dimethyl-3-phenyl-3,6-dihydropyridazine-1(2H)-carboxylate (356):** Following the procedure for the synthesis of 354, hydrazone 355 (145 mg, 0.39 mmol) was converted to 356 (101 mg) in 89% isolated yield.

**IR (neat):** 3285, 3062, 3028, 2977, 2918, 2885, 2861, 1695, 1679, 1492, 1453, 1389, 1366, 1240, 1173, 1139, 765, 700 cm$^{-1}$;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40 - 7.23 (m, 5 H), 4.61 (br. s, 1 H), 4.35 (br. s, 1 H), 4.29 - 4.10 (m, 1 H), 3.84 - 3.73 (m, 1 H), 1.78 (s, 3 H), 1.54 (s, 3 H), 1.24 (s, 9 H);

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 154.0, 139.6, 128.9, 128.4, 127.8, 125.8, 124.9, 77.4, 63.4, 28.1, 16.2, 15.8;

**HRMS-ESI(m/z):** calcd. for C$_{17}$H$_{24}$N$_2$NaO$_2$ [M+Na]+$^+$ 311.1741, found 311.1735.

**1-phenylphthahalazine (358):** To the tetrahydrophthalazine 287 (76 mg, 0.25 mmol) was added a 2.0 M solution of HCl in ether (2.4 mL) and the reaction was stirred at room temperature for 4 h. The mixture was then concentrated in vacuo to afford deprotected product, which was then
dissolved in anhydrous benzene (9.0 mL) and treated with DDQ (111 mg, 0.49 mmol) in one portion at room temperature. After stirring for 3 h, the reaction was concentrated in vacuo and purified via silica gel-based flash chromatography (0% to 3% MeOH in DCM with 0.2% Et$_3$N) to give product 358 (51 mg) in quantitative yield.

**IR (film):** 3058, 3030, 1544, 1447, 1387, 1368, 1354, 806, 762, 699 cm$^{-1}$;

**$^1$H NMR (300 MHz, CDCl$_3$):** $\delta$ 9.52 (s, 1 H), 8.09 - 8.00 (m, 2 H), 7.94 - 7.83 (m, 2 H), 7.77 - 7.72 (m, 2 H), 7.60 - 7.53 (m, 3 H);

**$^{13}$C NMR (101 MHz, CDCl$_3$):** $\delta$ 160.1, 150.7, 136.3, 132.8, 132.4, 130.2, 129.6, 128.7, 127.2, 126.8, 126.4, 125.6;

**HRMS-ESI(m/z):** calcd. for C$_{14}$H$_{11}$N$_2$ [M+H]$^+$ 207.0922, found 207.0921.

**tert-butyl 4-phenylphthalazine-2(1H)-carboxylate (357):** To the solution of tetrahydrophthalazine 287 (84 mg, 0.27 mmol) in anhydrous THF (2.5 mL) under nitrogen atmosphere was added NaH (54 mg, 1.35 mmol) in one portion at room temperature, followed by the addition of a 0.27 M solution of N-chlorosuccinimide (NCS, 90 mg, 0.67 mmol) in anhydrous THF. The reaction was then stirred at room temperature for overnight before being quenched with saturated aq. NaHCO$_3$ (20 mL) and extracted with EtOAc (30 mL). The organic layer was washed with brine (30 mL), dried over sodium sulfate and concentrated in vacuo to give the crude mixture which after silica gel-based flash chromatography (3% to 25% EtOAc in hexanes) afforded product 357 (60 mg) in 72% yield.
**IR** (film): 3062, 2978, 2931, 2833, 1699, 1453, 1390, 1322, 1234, 1149, 1122, 763, 699 cm⁻¹;

**¹H NMR (400 MHz, CDCl₃):** δ 7.74 - 7.70 (m, 2 H), 7.49 - 7.45 (m, 4 H), 7.35 - 7.30 (m, 3 H), 4.87 (s, 2 H), 1.61 (s, 9 H);

**¹³C NMR (101 MHz, CDCl₃):** δ 153.5, 152.5, 135.4, 132.5, 131.3, 129.2, 129.1, 128.4, 127.8, 126.5, 126.0, 125.6, 81.9, 44.3, 28.3;

**HRMS-ESI(m/z):** calcd. for C₁₉H₂₀N₂NaO₂ [M+Na]⁺ 331.1422, found 331.1423.

**Syntheses of pyrazolo phthalazine diones**

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{N}^\text{Boc} & \quad \text{N}
\end{align*}
\]

**General procedure:** To the solution of Boc-tetrahydrophthalazine (182 mg, 1 equiv) in DCM (1 mL) was added TFA (1 mL) at room temperature. After stirring for 30 min, the mixture was concentrated *in vacuo* to give the deprotected product, which was dissolved in anhydrous DCM (0.11 M of the deprotected product). To the solution was added 4-dimethylaminopyridine (5 equiv), and then a 0.21 M solution of malonyl chloride (1.2 equiv) in anhydrous DCM was added dropwise at room temperature. The reaction was stirred at room temperature for 3 h before being quenched with saturated aq. NH₄Cl (15 mL) and extracted with DCM (10 mL x 3). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to give crude mixture which was purified via silica gel-based flash chromatography (0% to 40% EtOAc in DCM) to afford the dione product.
5-(4-chlorophenyl)-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-1,3(2H)-dione (359):
Following the procedure above for the syntheses of pyrazolo phthalazine diones, Boc-tetrahydrophthalazine 292 (182 mg, 0.53 mmol) was converted to 359 (75 mg) in 45% isolated yield overall.

IR (film): 3026, 2927, 2855, 1739, 1700, 1695, 1490, 1454, 1409, 1394, 1327, 1231, 1091, 1015, 745, 699 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.42 - 7.29 (m, 5 H), 7.22 - 7.17 (m, 3 H), 6.37 (s, 1 H), 4.94 (d, \(J = 15.9\) Hz, 1H), 4.84 (d, \(J = 15.9\) Hz, 1H), 3.25 (d, \(J = 21.8\) Hz, 1H), 3.17 (d, \(J = 21.8\) Hz, 1H);

\(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 167.3, 166.2, 137.6, 134.7, 132.0 130.8, 129.6, 129.1, 128.7, 128.5, 128.4, 127.0, 57.8, 45.0, 37.6;

HRMS-ESI(m/z): calcd. for C\(_{17}\)H\(_{14}\)ClN\(_2\)O\(_2\) [M+H]\(^+\) 313.0744, found 313.0743.

8-methoxy-5-phenyl-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-1,3(2H)-dione (360):
Following the procedure above for the syntheses of pyrazolo phthalazine diones, Boc-
tetrahydrophthalazine 310 (114 mg, 0.33 mmol) was converted to 360 (68 mg) in 66% isolated yield overall.

**IR (film):** 3062, 3030, 3005, 2924, 2853, 1740, 1700, 1614, 1507, 1454, 1432, 1335, 1261, 1033, 749, 699 cm\(^{-1}\);

**\( ^1\)H NMR (400 MHz, CDCl\(_3\)):** \( \delta \) 7.33 - 7.28 (m, 3 H), 7.24 - 7.21 (m, 2 H), 7.13 (d, \( J = 8.4 \) Hz, 1 H), 6.87 (dd, \( J = 8.4, 2.6 \) Hz, 1 H), 6.80 (d, \( J = 2.6 \) Hz, 1 H), 6.37 (s, 1 H), 4.92 (d, \( J = 16.0 \) Hz, 1 H), 4.75 (d, \( J = 16.0 \) Hz, 1 H), 3.84 (s, 3 H), 3.20 (s, 2 H);

**\( ^{13}\)C NMR (101 MHz, CDCl\(_3\)):** \( \delta \) 166.7, 165.7, 159.5, 139.4, 130.1, 129.5, 128.9, 128.6, 127.9, 124.6, 114.5, 111.7, 57.8, 55.6, 44.9, 37.7;

**HRMS-ESI(m/z):** calcd. for C\(_{18}\)H\(_{16}\)N\(_2\)NaO\(_3\) [M+Na]\(^+\) 331.1059, found 331.1058.

**One-pot procedure from hydrazone 286 to protected diamine 372**

**\( \text{Br} \text{N} \text{Boc} \text{N} \text{Ph} \)**

\( \text{Toluene/hexanes (10 : 1)} \) \( \text{rt, 1.5 h} \)

\text{i) conc. HCl/dioxane (1 : 3) \( \text{rt, 1 h} \)}

\text{ii) 25 mol\% PtO\(_2\), 25 bar H\(_2\) MeOH, rt, 24 h; then Boc\(_2\)O, Et\(_3\)N, rt, 18 h}

**\( \text{NH} \text{Boc} \text{NH} \text{Boc} \)**

\( \text{286} \) \( \text{287} \) \( \text{372} \)

**tert-butyl (2-(((tert-butoxycarbonyl)amino)(phenyl)methyl)benzyl)carbamate (372):** To a 0.02 M solution of hydrazone 286 (156 mg, 0.4 mmol) in toluene (20 mL) was added (TMS)\(_3\)SiH (0.31 mL, 2.5 equiv) and a 1.0 M solution of Et\(_3\)B (2.0 mL, 5.0 equiv) in hexanes at room temperature. The reaction was stirred for 1.5 h under air atmosphere at room temperature, before being concentrated \textit{in vacuo} to afford crude product of 287. The crude mixture was then subjected to the mixture of dioxane/aqueous conc. HCl (3:1) (2 mL) and stirred for 1 h. After dilution with ethanol, the mixture was concentrated \textit{in vacuo} to afford the corresponding crude tetrahydrophthalazine hydrogen chloride salt.
The crude was then directly dissolved in MeOH (2 mL) and treated with PtO₂ (23 mg, 0.25 equiv). The reaction mixture was stirred under 25 bar hydrogen gas atmosphere at room temperature for 24 h, before purged with nitrogen gas and treated with triethylamine (0.33 mL, 6 equiv) and Boc₂O (420 mg, 4.8 equiv). The reaction was further stirred for overnight and concentrated in vacuo to afford crude mixture, which was purified via silica gel-based flash chromatography (2% to 20% EtOAc in hexanes) to afford the protected diamine 372 (93 mg) in 56% yield over four steps.

**IR (film):** 3326, 3063, 3030, 2978, 2931, 1690, 1511, 1496, 1454, 1391, 1366, 1250, 1167, 1044, 1020, 758, 733, 699 cm⁻¹;

**¹H NMR (300 MHz, CDCl₃):** δ 7.33 - 7.23 (m, 9 H), 6.17 (d, J = 6.4 Hz, 1 H), 5.39 - 5.27 (m, 2 H), 4.36 (d, J = 14.6 Hz, 1 H), 4.30 (d, J = 14.6 Hz, 1 H), 1.46 - 1.45 (m, 18 H);

**¹³C NMR (101 MHz, CDCl₃):** δ 156.0, 155.3, 141.5, 140.3, 136.8, 129.9, 128.8, 128.1, 128.0, 127.6, 127.4, 80.2, 79.5, 54.8, 42.3, 28.6;

**HRMS-ESI(m/z);** calcd. for C₂₄H₃₂N₂NaO₄ [M+Na]⁺ 435.2260, found 435.2261.

### Syntheses of Boc-protected diamines from tetrahydrophthalazines.

![Diagram of syntheses of Boc-protected diamines from tetrahydrophthalazines]

**General procedure for one-pot hydrogenation:** The Boc-protected tetrahydrophthalazine was treated with a mixture of dioxane/concentrated aq. HCl (3:1) (0.1 M) at room temperature and stirred till full conversion was observed by TLC, and was then concentrated in vacuo to afford the tetrahydrophthalazine hydrogen chloride salt. The salt was dissolved in MeOH to form a 0.1 M solution and was added the catalyst, PtO₂. The reaction was stirred under H₂ atmosphere (balloon
or high pressure) at room temperature for designated reaction time before being purged with N₂. Then the reaction mixture was added triethylamine (6 equiv) and di-tert-butyl dicarbonate (4 equiv), and it was stirred for overnight under N₂ at room temperature, followed by filtration through celite and concentration in vacuo to obtain crude mixture. Purification by silica gel-based flash chromatography (5 to 25% ethyl acetate in hexanes) afforded protected diamines.

**tert-butyl (1-(2-(((tert-butoxycarbonyl)amino)methyl)phenyl)-3-phenylpropyl)carbamate (369):** Following the hydrogenation procedure, with a H₂ balloon and 40 mol% PtO₂ for 24 h, the target protected diamine 369 (15 mg) was obtained in 49% yield overall.

**IR (film):** 3321, 3063, 3028, 2977, 2931, 2865, 1686, 1518, 1498, 1454, 1391, 1366, 1250, 1170, 1045, 1023, 751, 700 cm⁻¹;

**¹H NMR (300 MHz, CDCl₃):** δ 7.39 - 7.15 (m, 9 H), 5.95 (br. s, 1 H), 4.99 – 4.89 (m, 2 H), 4.43 (dd, J = 14.4, 6.9 Hz, 1 H), 4.15 (d, J = 14.4 Hz, 1 H), 2.71 - 2.59 (m, 2 H), 2.05 - 1.99 (m, 2 H), 1.46 (s, 9 H), 1.43 (s, 9 H);

**¹³C NMR (75 MHz, CDCl₃):** δ 156.0, 155.4, 141.0, 136.4, 130.3, 128.5, 128.3, 128.2, 127.6, 126.1, 125.5, 80.0, 79.0, 49.9, 42.2, 38.6, 32.7, 28.5, 28.4;

**HRMS-ESI(m/z):** calcd. for C₃₆H₅₆N₂NaO₄[M+Na]⁺ 463.2573, found 463.2570.
tert-butyl ((2-(((tert-butoxycarbonyl)amino)methyl)phenyl)(4-fluorophenyl)methyl)carbamate (373): Following the hydrogenation procedure with 25 mol% PtO₂ and 50 bar H₂ atmosphere, 373 (66 mg) was obtained in 67% yield overall.

IR (film): 3325, 3067, 2977, 2930, 1695, 1605, 1507, 1456, 1392, 1366, 1227, 1158, 1043, 1016, 755 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.38 - 7.37 (m, 1 H), 7.33 - 7.29 (m, 2 H), 7.21 - 7.16 (m, 3 H), 7.05 - 6.97 (m, 2 H), 6.13 (d, J = 6.6 Hz, 1 H), 5.38 (br. s, 1 H), 5.24 (br. s, 1 H), 4.36 (dd, J = 14.9, 6.5 Hz, 1 H), 4.24 (dd, J = 14.9, 4.5 Hz, 1 H), 1.45 - 1.44 (m, 18 H);

¹³C NMR (101 MHz, CDCl₃): δ 163.4, 161.0 156.0, 155.2, 140.1, 137.3, 136.6, 130.0, 129.1, 129.0, 128.2, 128.1, 127.6, 115.8, 115.5, 80.4, 79.5, 54.3, 42.2, 28.5;

HRMS-ESI(m/z): calcd. for C₂₄H₃₂FN₂O₄ [M+H]⁺ 431.2346, found 431.2341.

dert-butyl ((2-(((tert-butoxycarbonyl)amino)methyl)phenyl)(4-(tert-butyl)phenyl)methyl)carbamate (374): Following the hydrogenation procedure with 25 mol% PtO₂ and 25 bar H₂ for 3 days, the target diamine 374 (26 mg) was obtained in 37% yield.
IR (film): 3330, 3061, 2966, 2870, 1691, 1521, 1455, 1391, 1366, 1269, 1168, 1044, 1019, 757, 733 cm⁻¹;

¹H NMR (300 MHz, CDCl₃): 7.36 - 7.28 (m, 6 H), 7.12 (d, J = 6.4 Hz, 2 H), 6.13 (br. s, 1 H), 5.34 - 5.25 (m, 2 H), 4.40 - 4.26 (m, 2 H), 1.46 - 1.44 (m, 18 H), 1.31 (s, 9 H);

¹³C NMR (101 MHz, CDCl₃): δ 155.9, 155.1, 150.5, 140.3, 138.3, 136.5, 129.8, 127.9, 127.7, 127.2, 127.1, 125.6, 80.0, 79.3, 54.5, 42.1, 34.5, 31.3, 28.4;

HRMS-ESI (m/z): calcd. for C₂₈H₄₁N₂O₄ [M+H]⁺ 469.3066, found 431.3067.

**tert-butyl**

**((2-(((**tert**-butoxycarbonyl)amino)methyl)-5-fluorophenyl)(phenyl)methyl)carbamate (375):** Following the hydrogenation procedure with 25 mol% PtO₂ and 25 bar H₂ for 1 day and then 40 bar for 10 days, diamine 375 (26 mg) was obtained in 41% yield.

IR (film): 3325, 3064, 3031, 2978, 2931, 1689, 1495, 1453, 1392, 1366, 1247, 1160, 1044, 1021, 872, 732, 699 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ 7.36 - 7.28 (m, 4 H), 7.20 (d, J = 6.9 Hz, 2 H), 7.06 - 6.97 (m, 2 H), 6.11 (d, J = 6.2 Hz, 1 H), 5.35 - 5.26 (m, 2 H), 4.33 - 4.19 (m, 2 H), 1.46 (s, 9 H), 1.43 (s, 9 H);
\[\text{tert-buty}l\ (\text{trans-,(tert-butoxycarbonyl)amino)methyl}-4-
\text{methoxyphenyl}(\text{phenyl)methyl} \text{carbamate (376):}\]

Following the hydrogenation procedure with 25 mol% PtO\textsubscript{2} and 25 bar H\textsubscript{2} for 4 days, the target diamine 376 (42 mg) was obtained in 46% yield.

**IR (film):** 3334, 3062, 2977, 2852, 1691, 1500, 1454, 1392, 1366, 1271, 1248, 1165, 1045, 1020, 733, 699 cm\textsuperscript{-1};

\[\text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{):}\ δ 7.21 (m, 5H), 7.09 (d, J = 8.5 Hz, 1H), 6.91 (s, 1H), 6.79 (dd, J = 8.6, 2.7 Hz, 1H), 6.08 (br. s, 1H), 5.37 (br. s, 2H), 4.34 (dd, J = 15.1, 6.8 Hz, 1H), 4.23 (dd, J = 15.1, 4.5 Hz, 1H), 3.79 (s, 3H), 1.45 - 1.43 (s, 18H);

\[\text{\textsuperscript{13}C NMR (101 MHz, CDCl}_3\text{):}\ δ 159.2, 156.1, 156.0, 155.3, 141.9, 138.3, 132.4, 129.1, 128.7, 127.5, 127.2, 114.9, 113.5, 80.1, 79.5, 55.4, 54.4, 42.2, 28.5;

**HRMS-ESI(m/z):** calcd. for C\textsubscript{26}H\textsubscript{34}N\textsubscript{2}NaO\textsubscript{5} [M+Na]\textsuperscript{+} 465.2365, found 465.2369.
Chapter 6: Conclusions and Future Work

This thesis details the development of several radical synthetic methodologies that I completed during my PhD research. Overall, my research focused on two general themes: the development and investigation of new radical fluorination methodologies for the incorporation of medicinally-relevant fluorinated motifs (Chapter 2 and 3), and the development of new radical cyclizations for the syntheses of pharmaceutically-important nitrogen heterocycles and 1,4-diamines (chapter 4 and 5) (Scheme 6.1).

**Scheme 6.1.** Summaries of Chapter 2, 3, 4 and 5.

Through the two different themes of my research, this thesis fundamentally demonstrates the versatility of radical reactions in the innovation and development of new synthetic
methodologies, especially to provide superior efficiency in addressing the synthetic challenges that are unattainable for ionic reactions. Furthermore, the significance of radical reactions is well underlined in my research through the applications of radical methodologies to the syntheses of two pharmaceutically relevant motifs, organofluorine compounds and nitrogen heterocycles. This chapter will present our conclusions of each of the previous chapters, and outlooks for the future directions and potential applications.

6.1 Chapter 2: conclusions and future work

Chapter 2 describes the development of a new xenon difluoride-mediated radical fluorodecarboxylation methodology for the syntheses of aryl difluoromethyl ethers 165 from the corresponding 2-aryloxy-2-fluoroacetic acids 164 (Scheme 6.2). Overall, the yields of the desired difluoromethyl ethers ranged from moderate to high (52% to 80%), and the method utilized relatively mild reaction conditions and demonstrated high efficiency, compared to the existing synthetic methodologies (Chapter 2, Section 2.2).

This xenon difluoride-mediated method was ineffective for the syntheses of alkyl trifluoromethyl ethers, due to side reactions, such as aliphatic C-H fluorinations by xenon difluoride. Our studies on the direct hydrodecarboxylation of difluoroacetic acids to afford the corresponding difluoromethyl ethers were unsuccessful.
Considering the ability of xenon difluoride to promote radical fluorodecarboxylation of electron-deficient carboxylic acids, we hypothesized that it may be applied to the activation of trifluoroacetic acid (TFA) to form trifluoromethyl radicals, which are versatile radical species for direct trifluoromethylations. This process may be achieved through an oxidative radical decarboxylation of a xenon bis(trifluoroacetate) intermediate formed from xenon difluoride and trifluoroacetic acid. Preliminary studies in the Sammis laboratory have shown that xenon difluoride...
is able to effect radical fluorodecarboxylation of TFA. One of the potential applications of this new trifluoromethyl radical generation method is to react with diaryl disulfides to synthesize aryl trifluoromethyl thioethers, which are a pharmaceutically important motif.\textsuperscript{144}

![Scheme 6.3. Future work on XeF₂-mediated formation of the trifluoromethyl radical and its application.](image)

6.2 Chapter 3: conclusions and future work

This chapter details our studies on the mechanism of fluorine transfer in radical fluorinations by N-F reagents. Our study focused on detecting possible cationic intermediates during the fluorination of alkyl radicals. Two strategies to identify cationic intermediates were explored: carbocation rearrangement and carbocation capture (Figure 6.1).

![Figure 6.1. Two strategies to detect possible cation intermediates in radical fluorinations.](image)

The results of our studies on radical fluorination of peresters and carboxylic acids with NFSI and Selectfluor under photochemical or thermal conditions suggested that alkyl radicals generally react with N-F reagents through a fluorine atom transfer pathway. An SET process occurred to form a carbocation in the fluorination of a tertiary benzyl radical, as a tertiary benzyl alcohol was generated through water trapping the carbocation intermediate.
The studies on the silver-catalyzed radical fluorination of aliphatic acids revealed that Selectfluor reacts with alkyl radicals to form alkyl fluorides, through a fluorine atom transfer pathway. Additionally, rearranged ketone-containing products were observed in experiments with β-hydroxyl carboxylic acids. We proposed that carbocation intermediates were formed via SET between the alkyl radicals and high oxidation-state silver species, which subsequently led to the formation of ketones through carbocation rearrangement. However, due to the presence of different silver species in the reaction, our results did not provide correlation between carbocations formation and the fluorination processes. Thus, further studies will be focused on the investigation of the roles of carbocation intermediates in the formation of alkyl fluorides in the silver-catalyzed reaction.

A future direction of the mechanistic studies is to investigate the influence of the silver catalyst on the fluorination processes. In particular, it is important to probe whether a silver(II) fluoride was formed as an intermediate for fluorination. To investigate the relationship between carbocation intermediates and the fluorination process, a fluoride source and an oxidant, such as K₂S₂O₈, could be used to replace Selectfluor in the silver-catalyzed fluorination of aliphatic acids in order to exclude the fluorination by Selectfluor via fluorine atom transfer (Scheme 6.4). If alkyl fluorides were formed in the reaction, it would suggest the fluorination pathway through fluoride trapping. The potential application of fluoride trapping in silver-catalyzed radical fluorination processes may allow for the use of [¹⁸F]fluoride for [¹⁸F]radiolabelling.⁶⁹,¹⁶⁹

\[
\begin{align*}
R-\text{COOH} & \quad \xrightarrow{\text{cat. AgNO}_3, \text{Oxidant, F source}} \quad R-\text{F} \\
\end{align*}
\]

**Scheme 6.4.** Proposed fluorination using a fluoride source to trap the carbocation intermediate.
6.3 Chapter 4 and 5: conclusions and future work

Chapters 4 and 5 detail my research on the application of radical cyclizations for the syntheses of pharmaceutically relevant nitrogen heterocycles, such as tetrahydrophthalazine and its derivatives, tetrahydropyridazines and 1,4-diamines (Figure 6.2).

![Figure 6.2. Radical cyclization approaches to nitrogen-containing motifs.](image)

Phthalazine derivatives are important motifs present in pharmaceutically active molecules, but their syntheses using existing technologies display poor stereo- or regioselectivity (Chapter 4, Section 4.1 and 4.2). Chapter 4 describes the development of two synthetic protocols based on a 6-endo-trig radical cyclizations onto hydrazones, for the syntheses of substituted tetrahydrophthalazines from readily available aldehydes, hydrazides and ortho-bromobenzyl bromides. This key 6-endo-trig radical cyclization demonstrated excellent efficiency, robustness and tolerance of functional groups (Scheme 6.6). Our new protocols are able to regio- and stereoselectively access multi-substituted tetrahydrophthalazines, which provide effective solutions to the existing synthetic challenges.
Scheme 6.5. Scope studies for the syntheses of tetrahydrophthalazines through 6-endo-trig radical cyclizations onto hydrazones.

Not only does the 6-endo-trig radical cyclization onto hydrazones represent an effective method for the syntheses of tetrahydrophthalazine derivatives, but it also represents an underexplored endo radical cyclization onto C=N bonds (Chapter 4, Section 4.3). There have been many studies on the endo radical cyclizations onto imines, but there was only one previous example of 6-endo-trig cyclization onto hydrazones. This 6-endo-trig radical cyclization onto hydrazones is an important addition to the radical cyclization methodologies, and can provide further insights into the reactivity of hydrazones in radical reactions.
Chapter 5 described the application of the 6-endo-trig radical cyclization onto hydrazones for the syntheses of some other nitrogen heterocycles. We have demonstrated that the 6-endo-trig radical cyclization of 2-bromopyridine- and 3-bromoallyl-tethered hydrazones are able to afford tetrahydro-azaphthalazine and -pyridazines, respectively. We have also developed conditions for the conversion of tetrahydrophthalazines to dihydrophthalazines and aromatic phthalazines.

To demonstrate the pharmaceutical application of our synthetic protocols, we have tested our radical cyclization method in the process toward the syntheses of two drug analogs. The syntheses began with the radical cyclization to form the tetrahydrophthalazines, followed by a deprotection/diacylation sequence to afford pyrazolo phthalazine diones, which can be readily converted to the corresponding pyrazolo tetrahydrophthalazine drug analogs through reduction.

We conceived that tetrahydrophthalazines could be excellent precursors for 1,4-diamines. After extensive optimization, we successfully developed a one-pot process using a Pt-catalyzed hydrogenation reaction to synthesize 1,4-diamines from tetrahydrophthalazines (Scheme 6.6). Our preliminary studies on the substrate scope demonstrated that this method can access 1,4-diamines in moderate to good yields over three steps from Boc-protected tetrahydrophthalazines. Additionally, we have demonstrated that the radical cyclization and hydrogenation can be combined in a one-pot process to access Boc-protected diamine products from hydrazone starting materials in moderate yield over four steps.

![Scheme 6.6](image-url)

**Scheme 6.6.** Syntheses of Boc-protected diamines from tetrahydrophthalazines through hydrogenation.
A future direction of this 1,4-diamine synthesis project is to explore 1,4-diamine formation through nucleophilic substitution with concomitant N-N cleavage (Scheme 6.7). This is a redox-neutral process, which could use suitable nucleophiles, such as phenols or enolates, to access 1,4-diamines with selective functionalization on the nitrogen atoms.

**Scheme 6.7.** The N-N bond cleavage of tetrahydrophthalazines by nucleophilic substitution.

As phthalazinones are also important motifs in pharmaceutically active molecules, my colleagues, Jia Yi Mo and Cayo have successfully developed a one-pot process using our 6-endo-trig radical cyclization method for the syntheses of phthalazinones from N-benzoyl hydrazones through dihydrophthalazinone intermediates (Scheme 6.8). Further studies on the substrate scope and synthetic application are underway in the Sammis laboratory.

**Scheme 6.8.** One-pot process to access phthalazinones through radical cyclization.

Another future direction for this project is to apply a similar 6-endo-trig radical cyclization to oximes (Scheme 6.9). The preliminary results in the Sammis laboratory have shown that aryl and alkyl oximes can mainly afford the dehalogenated products through intermolecular HAT from TTMSS under our radical cyclization conditions. However, glyoxylate derived oxime was able to form the desired dihydrobenzooxazine as major product when protic solvents, such as methanol,
were used. The relevant studies are underway for the development of the first 6-endo-trig radical cyclization onto oximes.

Scheme 6.9. Future work on the 6-endo-trig radical cyclization of oximes.
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Appendices

Appendix A  Selected NMR Spectra for Chapter 2

1H NMR spectrum (300 MHz, CDCl3, 25 °C) of 164a:

![NMR Spectrum](image_url)
$^{19}$F NMR spectrum (282 MHz, CDCl$_3$, 25 °C) of 164a:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 164a:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 164b:

![1H NMR spectrum](image)

$^{19}$F NMR spectrum (282 MHz, CDCl$_3$, 25 °C) of 164b:

![$^{19}$F NMR spectrum](image)
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 164b:

![Chemical Shift (ppm)](image)

$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 164d:

![Chemical Shift (ppm)](image)
$^{19}$F NMR spectrum (282 MHz, CDCl$_3$, 25 °C) of 164d:

13C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 164d:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 164e:

$^{19}$F NMR spectrum (282 MHz, CDCl$_3$, 25 °C) of 164e:
$^{12}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 164e:

$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 170:
$^{19}F$ NMR spectrum (282 MHz, CDCl$_3$, 25 °C) of 170:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 170:
Appendix B  Selected NMR Spectra for Chapter 3

$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 180:

![1H NMR spectrum](image)

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 180:

![$^{13}$C NMR spectrum](image)
\(^1\)H NMR spectrum (300 MHz, CDCl\(_3\), 25 °C) of 181:

\[
\begin{align*}
\text{Chemical Shift (ppm)} & \\
7.45 & 7.45 \\
2.95 & 2.90 \\
1.57 & \\
1.14 & \\
\end{align*}
\]

\(^{13}\)C NMR spectrum (75 MHz, CDCl\(_3\), 25 °C) of 181:

\[
\begin{align*}
\text{Chemical Shift (ppm)} & \\
170.14 & \\
146.36 & \\
128.65 & 127.25 \\
83.87 & \\
73.10 & \\
63.94 & \\
30.64 & \\
\end{align*}
\]
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 205:

12C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 205:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 188:

13C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 188:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 189:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 189:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 190:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 190:
Appendix C  Selected NMR Spectra for Chapter 4

$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 289:

![NMR spectrum image]

Chemical Shift (ppm)
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 289:

Chemical Shift (ppm)

28.35  54.61  81.05  123.07  127.43  128.49  128.62  132.91  136.97  156.87

289
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 326:

\[ \begin{align*}
  &\text{N}^+\text{NHBOc} \\
  &\text{Ph} \quad \text{H}
\end{align*} \]

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 326:

\[ \begin{align*}
  &\text{N}^+\text{NHBOc} \\
  &\text{Ph} \quad \text{H}
\end{align*} \]
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 327:

\[
\text{Ph} - \text{NHBoc}
\]

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 327:

\[
\text{Ph} - \text{NHBoc}
\]
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 286:
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 286:
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 330:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 330:
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 333:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 333:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 334:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 334:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 336:

\[
\text{336}
\]

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 336:

\[
\text{336}
\]
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 338:

![H NMR spectrum](image)

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 338:

![C NMR spectrum](image)
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 341:

\[ 341 \]

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 341:

\[ 341 \]
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 342:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 342:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 345:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 345:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 349:

![NMR spectrum of 349](image1)

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 349:

![NMR spectrum of 349](image2)
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 287:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 287:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 290:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 290:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 291:

![H NMR spectrum](image)

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 291:

![C NMR spectrum](image)
\(^1\)H NMR spectrum (300 MHz, CDCl\(_3\), 25 °C) of 292:

\[
\text{Chemical Shift (ppm)}: 2.00, 1.02, 0.97, 4.91, 2.13, 7.33, 7.32, 7.31, 7.30, 7.28, 7.25, 7.22, 7.21, 6.85, 5.22, 4.88, 4.86, 4.81, 4.75, 1.41.
\]

\(^{13}\)C NMR spectrum (101 MHz, CDCl\(_3\), 25 °C) of 292:

\[
\text{Chemical Shift (ppm)}: 154.62, 139.35, 133.87, 132.50, 130.69, 130.40, 128.58, 127.92, 127.09, 126.54, 126.01, 81.03, 61.18, 46.23, 28.29, 21.18, 29.29.
\]
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 293:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 293:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 294:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 294:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 295:

13C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 295:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 296:

![NMR spectrum of 296](image)

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 296:

![NMR spectrum of 296](image)
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 297:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 297:
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 298:

![H NMR spectrum of 298](image)

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 298:

![C NMR spectrum of 298](image)
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 299:

\[ \text{299} \]

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 299:

\[ \text{299} \]
$^{1}H$ NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 300:

$^{13}C$ NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 300:
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 301:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 301:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 302:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 302:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 303:

![1H NMR spectrum](image)

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 303:

![13C NMR spectrum](image)
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 304:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 304:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 305:

$$\text{Chemical Shift (ppm)}$$

1.99 2.38
1.00 1.01
9.09 8.99

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 305:

$$\text{Chemical Shift (ppm)}$$

155.15 135.36 132.36 128.73 126.83 126.62 125.25 80.48 66.17 45.23 36.56 28.56 27.98
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 306:

![1H NMR spectrum](image)

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 306:

![13C NMR spectrum](image)
\(^1\)H NMR spectrum (400 MHz, CDCl\(_3\), 25 °C) of **307**:

\[
\begin{array}{c}
\text{HN} \quad \text{N} \quad \text{Boc} \\
\text{NH} \quad \text{Ph} \\
\text{307}
\end{array}
\]

\[^{13}\text{C} \text{NMR spectrum (101 MHz, CDCl}_3\), 25 °C) of **307**:

\[
\begin{array}{c}
\text{HN} \quad \text{N} \quad \text{Boc} \\
\text{NH} \quad \text{Ph} \\
\text{307}
\end{array}
\]
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 308:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 308:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 309:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 309:
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 310:

![H NMR spectrum](image)

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 310:

![C NMR spectrum](image)
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 311:

![H NMR spectrum](image)

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 311:

![C NMR spectrum](image)
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 313:

$^1$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 313:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 316:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 316:
Appendix D  Selected NMR Spectra for Chapter 5

$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 350:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 350:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 353:

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 353:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 355:

![H NMR spectrum](image)

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 355:

![C NMR spectrum](image)
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 351:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 351:
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 354:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 354:
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 356:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 356:
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 357:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 357:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 358:

$^{12}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 358:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 359:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 359:
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 360:

\[ \text{Chemical Shift (ppm)} \]

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 360:

\[ \text{Chemical Shift (ppm)} \]
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 372:

\[
\begin{align*}
&\text{NHBoc} \\
&\text{NHBoc}
\end{align*}
\]

Chemical Shift (ppm)

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 372:

\[
\begin{align*}
&\text{NHBoc} \\
&\text{NHBoc}
\end{align*}
\]

Chemical Shift (ppm)
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 369:

![H NMR spectrum](image)

$^{13}$C NMR spectrum (75 MHz, CDCl$_3$, 25 °C) of 369:

![C NMR spectrum](image)
$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 373:

![H NMR spectrum of 373](image)

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 373:

![C NMR spectrum of 373](image)
$^1$H NMR spectrum (300 MHz, CDCl$_3$, 25 °C) of 374:

$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 374:

$^1$H NMR spectrum (400 MHz, CDCl$_3$, 25 °C) of 375:
\( ^{13} \text{C} \) NMR spectrum (101 MHz, CDCl\(_3\), 25 °C) of 375:

\( ^1 \text{H} \) NMR spectrum (400 MHz, CDCl\(_3\), 25 °C) of 376:
$^{13}$C NMR spectrum (101 MHz, CDCl$_3$, 25 °C) of 376:

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