APPROACHES TO HYDROCARBON FUNCTIONALIZATION USING HETEROATOM-CENTERED RADICALS

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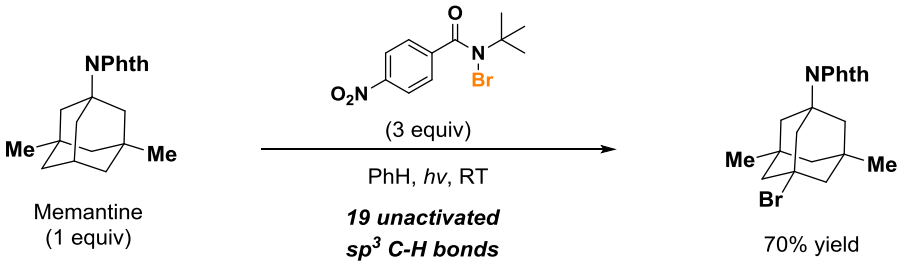
ABSTRACT

RYAN KEMPER QUINN: Approaches to Hydrocarbon Functionalization Using Heteroatom-Centered Radicals
(Under the direction of Erik J. Alexanian)

I. Intermolecular Aliphatic C-H Functionalizations

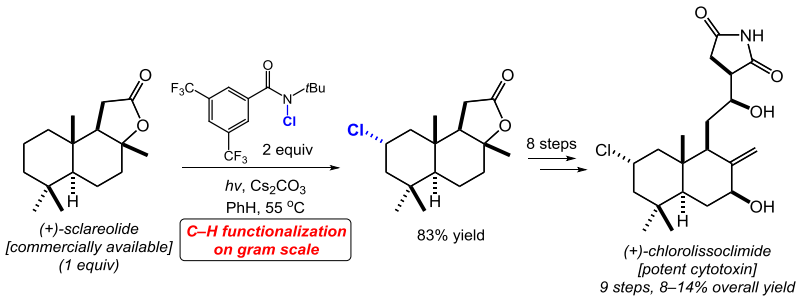
An overview of intermolecular aliphatic C-H functionalization reactions is presented. The historical perspective and current state-of-the art methodologies are presented in the areas of C-H oxidation, halogenation, and amination reactions.

II. Aliphatic C-H Bromination Using *N*-Bromoamides



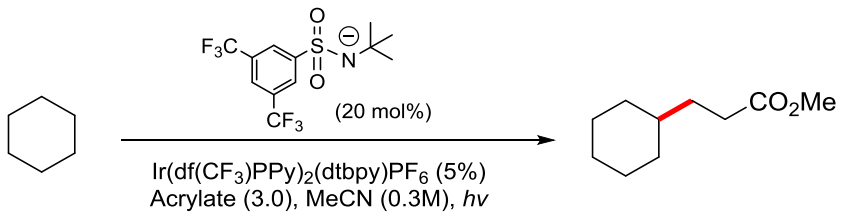
A site-selective approach for C-H bromination is outlined. The reactions proceed efficiently with 1 equivalent of alkane substrate. Selectivity, scope and mechanism are discussed.

III. Aliphatic C-H Chlorination Using *N*-Chloroamides



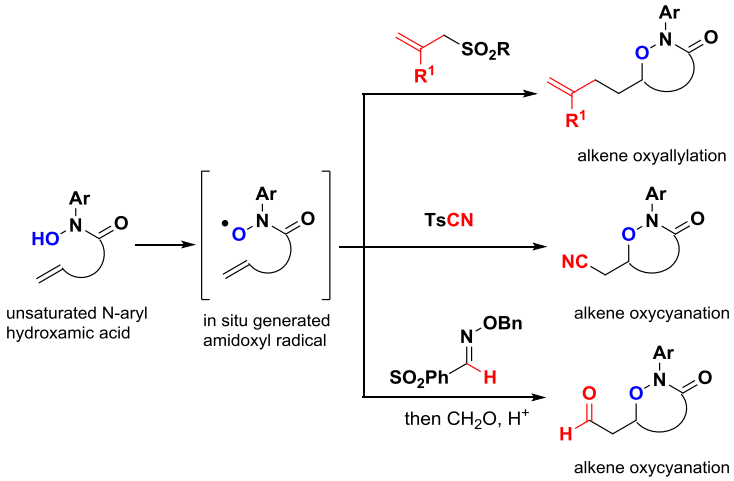
A site-selective approach for C-H chlorination is outlined. The reaction shows improved efficiency and scope compared to the bromination study. An application toward the synthesis of *(+)-chlorolissoclimide* is included.

IV. Catalytic C-H Functionalizations Using Amidyl Radicals



Efforts to convert the C-H chlorination to a catalytic variant are summarized; promising lead results are highlighted. Generation of amidyl radicals using proton coupled electron transfer is also discussed. Initial promising results in this area are highlighted.

V. Alkene Carbooxygenations Using Hydroxamic Acids



A radical mediated approach to alkene carbooxygenation using hydroxamic acids is described. These reactions deliver a divers set of carbon-carbon bond forming reactions to a variety of alkene substrates.

ACKNOWLEDGEMENTS

The axiom "no man is an island" applies as much in science as in other walks of life. Accordingly I would like to thank all those who have helped me attain my goals. Firstly, I would like to acknowledge my PhD advisor, Prof. Erik J. Alexanian, for his guidance, patience, and intellectual contributions to my doctoral research projects. Erik's guidance has helped grow from a student who possesses a love for synthetic organic chemistry into a scientist who has a more complete understanding of what it takes to develop new and impactful chemical reactions – and, more importantly, what it takes to make a meaningful contribution to our field.

Secondly, I would like to thank others who took the time to personally serve as my mentors in helping me develop the skills of an organic chemist. My undergraduate research advisor, Prof. Bianca R. Sculimbrene, taught me how to be more intellectually curious and appreciate the value of basic research. Dr. Valerie Schmidt, Andy Bruscoe, and Kyla Bloome each served to varying degrees as my graduate student mentors. Together they helped me succeed as a graduate student by teaching how to run and analyze chemical reactions, read and understand the chemical literature, and think more critically about my research projects. I would also like to thank all members of the Alexanian group past and present.

Lastly I would like to thank my parents, Michael Quinn and Theresa Kemper, and my brothers McLean Quinn and Carter Quinn. The space here is not nearly adequate to describe how grateful I am to them. Their unwavering encouragement, support and companionship has propelled me to heights I couldn't have imagined.

To Dad, I miss you every day.

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LIST OF ABBREVIATIONS AND SYMBOLS

μ	micro
°C	degrees Celsius
Δ*f*H°	heat of formation
1H NMR	proton nuclear magnetic resonance spectroscopy
13C NMR	carbon nuclear magnetic resonance spectroscopy
4 Å MS	4 angstrom molecular sieves
Ac	acetate
Ac2O	acetic anhydride
acac	acetylacetone
AcOH	acetic acid
AD	asymmetric dihydroxylation
atm	atmospheres
Bn	benzyl
br s	broad singlet
BQ	benzoquinone
Bu	butyl
Bz	benzoyl
C-H	carbon-hydrogen bond
cat.	catalytic amount or catalyst
cm-1	wavenumbers
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DLP	dilauroyl peroxide
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
e-	electron
ee	enantiomeric excess
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
Et2O	diethyl ether
et al.	and others
etc.	et cetera
EtN*i*Pr2	*N,N,N*-diisopropyl-ethylamine
EtOAc	ethyl acetate
h	hours
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry

hν	light
Hz	hertz
i.e.	in other words
iPr	iso-propyl
IR	infared spectroscopy
J	coupling constant
kcal	kilocalorie
k	rate
LDA	lithium diisopropylamide
LDE	lithium diethylamide
LRMS	low resolution mass spectroscopy
m	multiplet
Mbs	4-methoxybenzenesulfonyl
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	mega hertz
min	minute(s)
mg	milligram
mL	milliliter
mmol	millimole
modp	bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)
NBS	*N*-bromosuccinimide

nBuOAc	butyl acetate
NHC	*N*-heterocyclic carbene
nPrOH	butyl acetate
Ns	4-nitrobenezenesulfonyl
OTf	triflate, trifluoromethanesulfonate
Ph	phenyl
Phth	phthalimide
PPh3	triphenyl phosphine
ppm	parts per million
PTFE	polytetrafluoroethylene, teflon
p-Tol	4-methyl phenyl
q	quartet
qd	quartet of doublets
quant	quantitative
R	generic organic group
rt	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
tBu	*tert*-butyl
tBuOH	*tert*-butanol

td	triplet of doublets
TEMPO	tetramethylpiperidine-*N*-oxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPP	tetraphenylporphyrin
Ts tosyl,	4-toluenesulfonyl

1 CHAPTER ONE

Intermolecular Aliphatic C-H Functionalizations

1.1 Introduction

As a general class of chemical reactions, transformations that selectively functionalize aliphatic C-H bonds have significant promise for streamlining organic synthesis. Such reactions will expedite access to new therapeutic agents and lead to analogues with improved activities. Currently a wide variety of methods exist to selectively functionalize *aryl* sp^2 C-H bonds. Few methods of preparative value exist, however, to selectively functionalize *aliphatic* sp^3 C-H bonds. Most current reactions of this type are limited in their synthetic value due to low reaction yields, unpredictable selectivity, and the requirement of large excess of the alkane substrate.[1]

Saturated hydrocarbons are the main constituents of oil, natural gas and other major chemical feedstocks. Additionally, sp^3 C-H bonds are present in nearly every organic molecule. Therefore, the ability to treat such bonds as *functional groups* that can be predictably manipulated will revolutionize the field of organic synthesis as described above. The relative strength and inertness of C-H bonds compared to other bonds in organic molecules renders them generally unreactive. Furthermore, most aliphatic C-H bonds fall within an energetic window of 7 kcal/mol (91-98 kcal/mol).[2] Consequently, it is a significant chemical challenge to develop a reagent or catalyst reactive enough to react with the inert C-H bond, but selective enough to preferentially react at one specific C-H bond within the molecule. A number of enzymes are known to participate

in highly selective C-H functionalizations, though their reactivity is highly substrate specific.[3,4] The long term goal of this field is the development of aliphatic C-H functionalization reactions that possess enzyme-like selectivity, but can be applied to a broad class of hydrocarbon substrates.

1.2 Background

A number of protocols exist for the conversion of aliphatic C-H bonds to more synthetically useful C-C or C-Heteroatom functionality. Among the strategies employed to achieve this goal include the use of highly reactive radical intermediates, biomemmetic transition-metal catalysts, highly strained heterocycles, and in some cases direct oxidation conditions.[5] Free-radical halogenation, which converts alkanes to their corresponding alkyl bromides or chlorides, has been known since the 1930s. These traditional reactions often possess poor site-selectivity, low yields and uncontrolled reactivity.[6] Directing groups are often employed in C-H functionalization reactions to circumvent the issue of selectivity. This review will focus on the reagents and strategies for affecting alkane functionalization without the use of a directing group. More recently, however, synthetically useful C-H oxidations, halogenations, aminations, and alkylation protocols have begun to appear in the chemical literature. The historical perspective as well as the current state-of-the-art in each of these areas is discussed below.

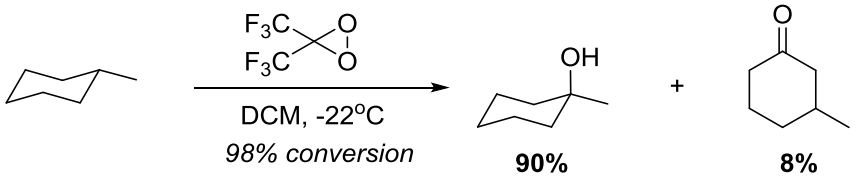
1.2.1 Aliphatic C-H Oxidation

The formation of aliphatic ketones and alcohols via direct C-H oxidation is one of the most widely explored areas in C-H functionalization chemistry. Nature relies on enzymatic processes to break C-H bonds, often replacing them with stronger O-H bonds. The iron center in P450 enzymes enables the oxidation of these notoriously strong bonds.[7] Chemists have invested significant efforts in emulating this reactivity: first through the use of strained and highly reactive oxacycles and later through more intentional mimicry of the P450 system using iron or other transition metal

complexes. There are two major challenges present in modern aliphatic C-H oxidation: (1) controlling the site-selectivity of these highly reactive reagents, and (2) preventing over-oxidation of C-H hydroxylation products to aliphatic ketones or aldehydes.

In the late 1970s a class of organic peroxides was developed that possess great synthetic potential due to inherent energy stored in the compounds. The family of reagents are the smallest endoperoxides containing carbon, the dioxirianes. These highly reactive compounds can be used in a number of oxygen-transfer reactions with olefins, ketones, alkynes, isocyanates and enol ethers. Curci and coworkers expanded the oxidizing power of dioxirane compounds toward the goal of direct aliphatic alkane oxidation. Alkane substrates subjected to oxidation with trifluorodioxirane (TFDO) solutions in DCM yield a mixture of aliphatic alcohols and ketones.

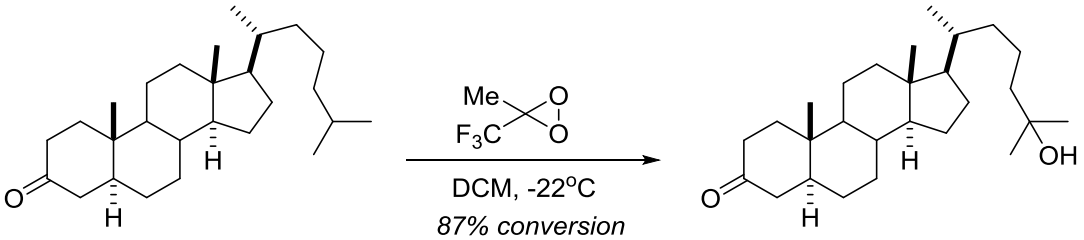
Figure 1-1. Dioxirane oxidation of methylcyclohexane



Curci, *JACS,* **1989**, 6749.

Curci described the preference for oxidation to occur at the most electron rich sites in the molecule, resulting in somewhat selective reactions at tertiary C-H bonds to give tertiary alcohol products (**Figure 1-1**). Oxidation by TFDO at methylene sites gives ketone products.[8] The preference for tertiary hydroxylation with dioxiranes is so strong, single products can be formed using complex molecules as the alkane substrate (**Figure 1-2**).[9]

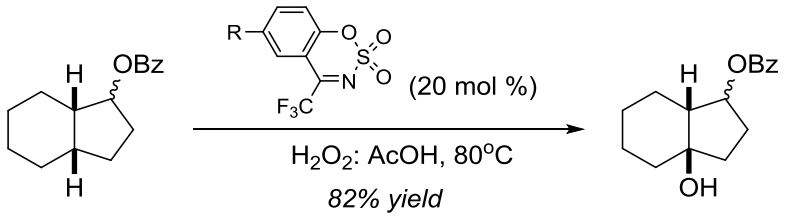
Figure 1-2. Dioxirane oxidation of steroid substrate.



Curci, *JOC,* **1992**, 2182.

Later strategies for alkane oxidation draws on initial information disclosed by Curci and coworkers, but attempt to generate the active oxidant *in situ* or modulate its identity to improve its stability. Justin Du Bois developed a system based on this idea using a benzoxathiazine organocatalyst. In the presence of acetic acid and peroxide the benzoxathiazine is converted to an oxaziridine, the active oxidant in the reaction (**Figure 1-3**). The reactivity and selectivity is similar to dioxirane oxidation, though the authors claim an organocatalytic manifold should allow the

Figure 1-3. Alkane hydroxylation using benzoxathiazine organocatalyst



Du Bois, *ACIE,* **2009**, 4513.

properties of the catalyst to be tuned toward the desired reactivity.[10,11] More recently, similar reactivity was demonstrated using trifluoroacetophenones as organocatalysts that generate dioxiranes *in situ*. The reaction proved effective with a number of trifluroacetophoenones possessing differing aromatic substitutions and basic alkane substrates.[12]

The other major strategy for alkane oxidation involves the use of transitions metal catalysts meant to mimic the reactivity of enzymes like cytochrome P450 discussed above. These biomimetic systems often rely on oxidized Fe or Mn complexes as the active species that can be regenerated using a stoichiometric oxidant like oxygen or peroxide. While this area of chemistry has become a popular area of investigation in the last decade, the ability of Fe Gif-type systems to oxidize saturated hydrocarbons to ketones via an Fe(V) oxenoid species has been known for some time.[13, 14] In 1990, Barton reported the Gif^{IV} system was effective for the conversion of cycloalkanes to the corresponding monoketone (**Table 1-1**).[15] Similar reactivity is also possible with Mn based catalysts.[16]

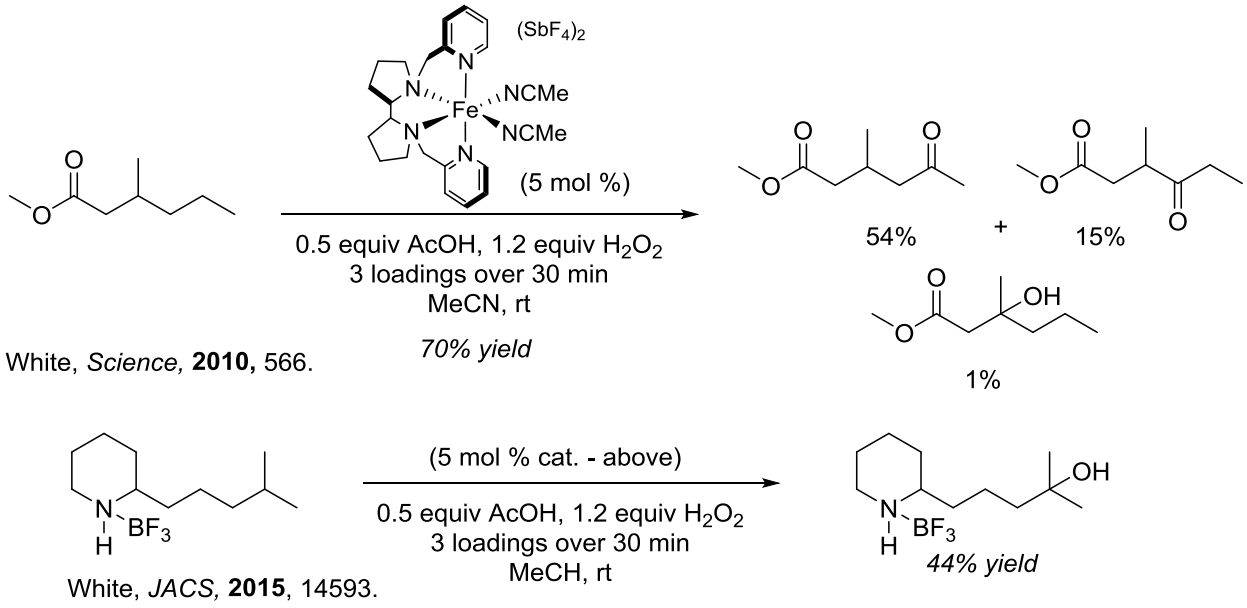
Table 1-1. Early Fe and Mn oxidation systems (cyclohexane to cyclohexanone)

Entry	Oxidation Conditions	Yield	Ref
1	$MnClO_4$-H_2O (0.1%) Pyridine-2-carboxylic acid (1.0%) H_2O_2 (4.0 equiv)	34	34
2	Gif^{IV} (Fe^{III} cat. Zn^o) Pyridine-Acetic acid Oxygen	32	13
3	Fe^{III} Porphyrin (cat) Iodosylbenzene (1 equiv)	8	14

Improved transition metal systems for alkane oxidation have been recently developed, the most prominent of which was discovered by White and coworkers. An (Fe)-based catalyst was developed that works in combination with hydrogen peroxide (H_2O_2) to oxidize a range of alkane substrates. The electrophilic [Fe(II)(mep)$(CH_3CN)_2$] $(SbF_6)_2$ catalyst gives regioisomeric mixtures of ketone and alcohol products. A prototypical example of the reactivity is shown in **Figure 1-4.** Oxidation is favored at the most electron rich site in the molecule.[17,18] The steric nature of the catalyst also imparts some selectivity on the reaction; changing the ligand structure around the Fe

center results in modest changes in site selectivity.[19] The substrates are mostly confined to unfunctionalized alkanes, esters, and protected alcohols, thought White recently reported that heteroatom-containing substrates can also be tolerated through pre-complexation with lewis acids (**Figure 1-4**).[20]

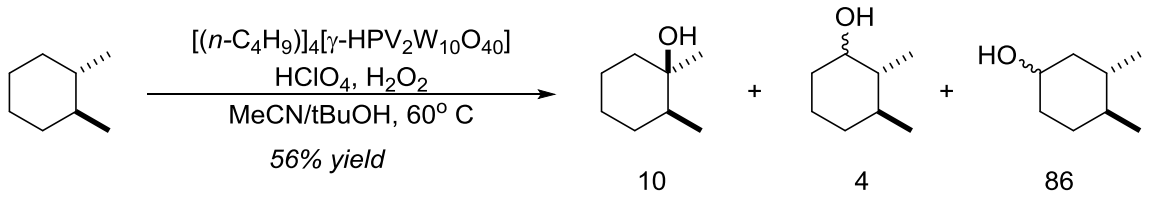
Figure 1-4. Biomimetic oxidation of alkanes using an iron catalyst



It is clear that the both the dioxirane chemistry and the metal-oxo chemistry described above prefer to react at electron rich, tertiary C-H bonds. In 2010, Mizuno disclosed a system to overcome this bias. Using a bulky polyoxotungstate catalyst in place of the (Fe) based catalyst shown above, Mizuno and coworkers observe significantly improved steric selectivities. Mizuno shows that oxidation is preferred at methylene sites that are the least congested in the molecule. Additionally the polyoxotungstate system does not encounter issues with over oxidation to the ketone. The selectivity for hydroxylated product possesses multiple advantages: (1) if the alcohol product is desired, additional redox manipulations can be circumvented (2) the potential for

asymmetric C-H functionalization exists. While only unfunctionalized alkane substrates are shown, Mizuno's chemistry represents a significant advance in the field of C-H oxidation.[21]

Figure 1-5. C-H hydroxylation using a polyoxotungstate catalyst

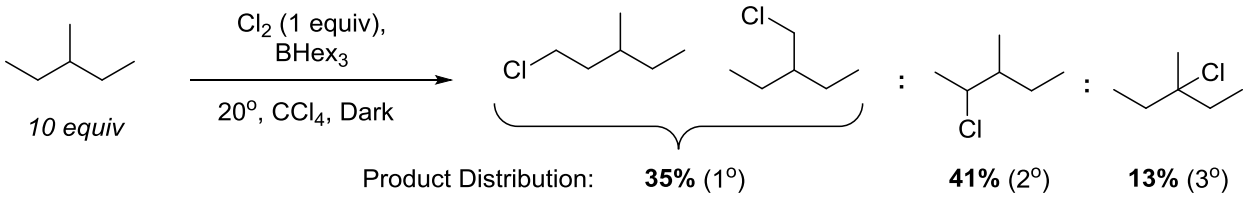


Mizuno, *Nat. Chem.,* **2010,** 478.

1.2.2 Aliphatic C-H Halogenation

Compared to oxygenation, the methods for affecting C-H halogenation are significantly limited. Most existing alkane halogenations require multiple equivalents of substrate or result in poor site-selectivities. Light-initiated radical chlorination of alkanes is one of the oldest reactions in synthetic chemistry and still used industrially for the chlorination of methane.[22] Free radical chlorination involves the formation of highly reactive chlorine radicals which indiscriminately react with most hydrocarbon substrates. Therefore, free-radical chlorination generally provides near statistical mixtures of primary (1°), secondary (2°), and tertiarty (3°) alkyl halide products. An example from Arase and coworkers demonstrates the low site-selectivity of free radical

Figure 1-6. Free radical chlorination of 3-methyl pentane



Arase *Chem. Lett.,* **1984,** 195.

using 3-methyl pentane as a substrate and a trialkyl borane initiator (**Figure 1-6**).[23] It has been suggested by Hass that the low selectivity of such species results from the fact that the rate of

abstraction is competitive with the rate of diffusion of chlorine atoms in solution, and that once a chlorine atom is in contact with a hydrocarbon molecule, it is predisposed to react there rather than seek out a more reactive site.[24] This general principle greatly limits the synthetic utility of aliphatic chlorination using chlorine radical except in the cases where (1) only one type of hydrogen is available (2) where one wishes to introduce the chloride functionality randomly (3) or one wishes to discard the majority of products formed in favor of the desired product.

Significant efforts have been made to modulate selectivity of free radical chlorination through the inclusion of additives, alternative chlorine sources, as well as solvent modifications. The low selectivity of the parent reaction is due to the exothermic C-H abstraction of the chlorine radical. Therefore, changing the abstracting agent often changes the selectivity of the reaction.

Table 1-2. Selectivity of various free radical chlorination conditions

Entry	Reagent	Relative C-H Reactivity (1^o/ 2^o/ 3^o)
1	Cl_2, *hv*	1:3.6:4.2
2	Cl_2, *hv,* benzene	1:10:50
3	Cl_2O, *hv*	1:12:24
4	t-BuOCl, *hv*	1:8:44
5	$SOCl_2$, initiator	1:10:50
6	NCS, initiator	1:2.5:4
7	$PhICl_2$, *hv*	1:20:350

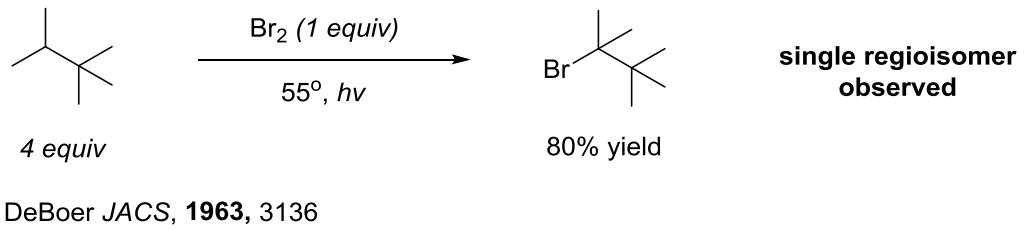
Poutsma *Methods in Free Radical Chemistry,* **1969**.

This low inherent selectivity can partly be overcome by using sulfuryl chloride, N-chlorosuccinimide, tert-butyl hypochlorite, trichloromethanesulfenyl chloride, trichloromethanesulfonyl chloride, (dichloroiodo)benzene [dichloro(phenyl)-λ3-iodane], or chlorine monoxide in place of molecular chlorine. **Table 1-2** shows how each of these

modifications alters the selectivity of the reaction, generally increasing the balance of tertiary alkyl chloride product formed by stabilizing the intermediate radical species formed in the reaction.[25]

Free-radical halogenation with liquid bromine possess a greater inherent selectivity than the related chlorination reaction. Due to the endothermic nature of the C-H abstraction by bromine radical the reaction can be highly selective for the weakest C-H bond in the molecule.[26] The reaction, therefore, tends to give favorable site selectivity for tertiary positions, or activated allylic or benzylic positions as in the Wohl-Zeigler reaction.[27] DeBoer showed that when 2,2,3-

Figure 1-7. Regioselectivity of free-radical bromination



trimethylbutane is subjected to standard free radical bromination conditions the tertiary alkyl bromide is formed as a single regioisomer (**Figure 1-7**). The same reaction proceeds with sluggish efficiency if only primary or secondary C-H bonds are present in the alkane substrate.[28] Comparable to chlorination with molecular chlorine, modifications can be made to standard free-radical bromination conditions to modulate the selectivity of the reaction. The bromination of adamantane is shown to illustrate this point (**Table 1-3**). Reactions that generate bromine radical (**Table 1-3**, Entries 1, 2 and 3) exhibit low to moderate differentiation between the secondary and tertiary positions of adamantane. The electron rich nature of the substrate and the high stability of the carbon centered radicals formed at both the tertiary and secondary positions limits the substrate bias for regioselectivity compared to a typical acyclic alkane substrate (**Figure 1-7**). More bulky, electrophilic radicals (**Table 1-3**, Entries 3, 4, and 5) show a significantly greater preference for

formation of the tertiary adamantly bromide, the least sterically hindered position in the molecule.[29]

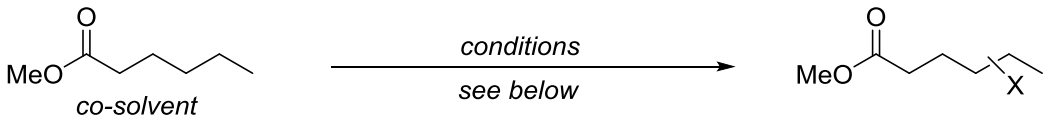
Table 1-3. Regioselectivity in the free radical bromination of adamantane

Entry	Reagent	Solvent, temp.	Relative C-H Reactivity (3^o: 2^o)
1	NBS, initiator	PhCl, 95°C	2.5
2	NBS + Br_2, *hv*	DCM, 25°C	5.8
3	Br_2, *hv*	CCl_4, 45°C	5.6
4	CBr_4, PTC	DCM, 25°C	30
5	CH_2Br_2, initiator	CH_2Br_2, 95°C	9.0
6	$BrCCl_3$, initiator	$BrCCl_3$, 95°C	27

Schreiner *Handbook of C-H Transformations,* **2005**.

Nitrogen-centered radicals have also been employed toward the goal of aliphatic halogenation. In the 1960s Minisci and coworkers developed a system that employs nitrogen-centered cation radicals to affect alkane chlorination and bromination. Minisci's halogenation reaction is essentially an intermolecular variant of the Hoffman-Loeffler-Freytag reaction, a method used commonly for the synthesis of cyclic amines via a remote C-H functionalization.[30] The alkane is dissolved in concentrated sulfuric acid and subjected to halogenation with dimethyl haloamine. Due to the electrophilic nature of the cation radical abstracting species, reaction occurs preferentially at the most electron rich position of the alkane substrate (**Table 1-4**). Minisci observes remarkable selectivity for the δ position using light (**Table 1-4**, Entries 1 and 4) and metal mediated (**Table 1-4**, Entries 2 and 3) initiation methods. Both aliphatic chlorination[31] and bromination[32] proceed with similar selectivities, though no chemical yields are reported and the alkane substrate is used as co-solvent in the reaction.

Table 1-4. Halogenation of methylhexanoate using *N*-haloamines



entry	reagents	α MeO_2C—CH_2—	β —CH_2—	γ —CH_2—	δ —CH_2—	ω —CH_3
1	15% AcOH, H_2SO_4, Me_2NCl	—	4.7	13.5	78.0	3.9
2	$FeSO_4$, H_2SO_4, Me_2NCl	—	0.7	6.3	87.3	5.7
3	Cu_2SO_4, H_2SO_4, Me_2NCl	—	0.3	4.7	89.4	5.6
4	15% AcOH, H_2SO_4, Me_2NBr	—	0.3	4.7	89.4	5.6
5	HNO_3, Br_2, NHPI (cat), AcOH, Δ	—	0.3	4.7	89.4	5.6

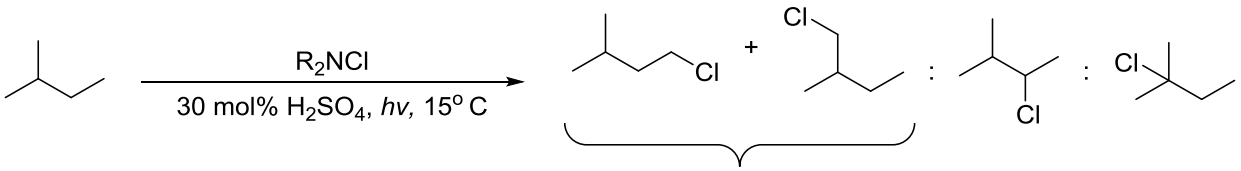
Minisci, *Tetrahedron Lett.* ***1967,*** 2207.

More recently Minisci and coworkers adapted their aliphatic halogenation system to exclude the use of haloamines in favor of electrophilic phthalimido-N-oxy (PINO) radical as the abstracting agent (**Table 1-4**, Entry 5). PINO radical is generated *in situ* from N-hydroxyphthalimide (NHPI). The reaction proceedes with preference for bromination at the δ position in greater than 89% selectivity. The use of nitric acid and low reaction conversions (*ca* 30-40%), however, limit the greater synthetic utility of the reaction.[33]

In the wake of Minici's initial reports on alkane halogenation using dimethyl haloamines, Deno and coworkers explored the effect of modulating the alkyl group on the haloamine as a means of altering site-selectivity. Seven different symmetrically and differentially substituted chloroamines were screened against alkane substrates that contain primary, secondary and tertiary C-H bonds. Shown below are selected results for the chlorination of isopentane with dicyclohexyl chloramine and *tert*-buty-*tert*-amyl chloroamine respectively (**Figure 1-8**). The later of the two halogenating agents is more sterically encumbered, resulting in a 17% reduction in the amount of 2-chloro-2-methyl butane product formed. Similar to the work reported by Minisci, the alkane

substrate is used as solvent, no yields are given, and concentrated acid is needed to generate the active cation radical abstracting species.[34]

Figure 1-8. Sterically hindered chlorinating agents

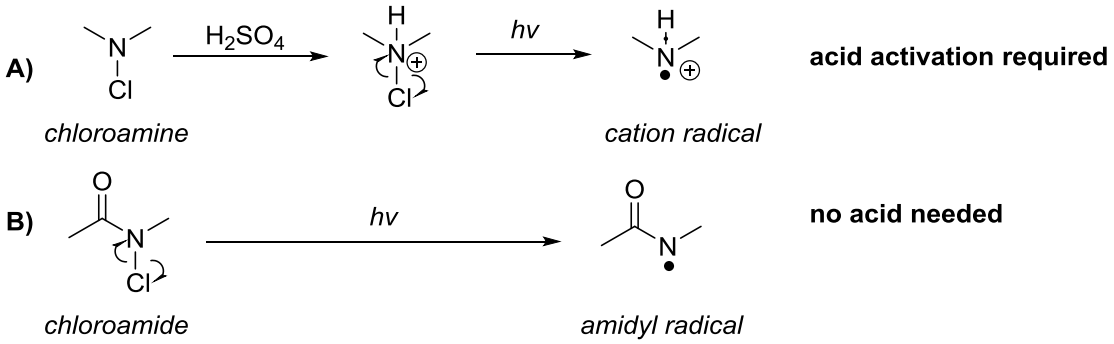


ratio of products:				
	R= Cy, Cy	17.0	44.4	39.6
	R= tBu, t-amyl	16.0	61.4	22.7

Deno, *JACS,* **1971**, 2065

During the same time-frame, investigation into haloamides and sulfonamides as competent alkane halogenating agents was also under way. Greene and coworkers disclosed both inter-and intramolecular alkane halogenations using bromo- and chloroamides, while Hickinbottom disclosed similar reactivity using *N*-chlorsulfonaimde reagents. It is notable that in both studies the use of acid was not required to activate the electrophilic C-H abstracting agent (**Figure 1-9**).

Figure 1-9. Generation of C-H abstracting agents in N-halo chemistry



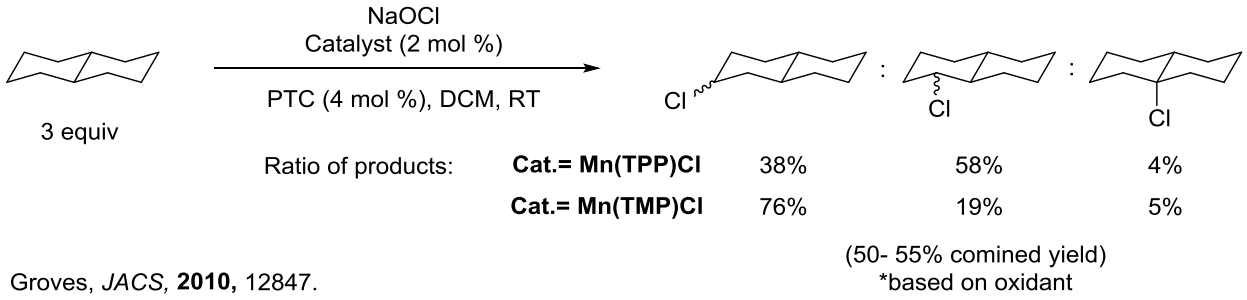
Greene, *JOC*, **1975,** 2186

Hickinbottom reported alkane chlorination using chlorosulfonamides, noting a mild preference for functionalization at secondary over primary C-H bonds. The selecitivities reported were comparable to reaction with molecular chlorine and sulfuryl chloride; no yields were reported.[35]

Greene reported yields for the chlorination of cyclohexane as high as 88% with respect to haloamide, though multiple equivalents of the alkane substrate were used.[36] The exclusion of concentrated acid in both methods is promising in both methods, however, further synthetic applications were not investigated.

Recently, biomimetic approaches to alkane halogenation have emerged as a synthetically viable strategy to achieve this goal. Groves and coworkers developed a Mn-porphyrin complex that functions as a catalyst for aliphatic chlorination in the presence of stoichiometric hypochlorite (Error! Reference source not found.). A Mn (V) dioxo or oxohydroxyo porphyrin complex is proposed as the species responsible for the C-H abstraction. The majority of the examples shown effect alkane chlorination, though the authors show that the addition of sodium bromide allows the formation

Figure 1-10. Mn-Porphyrin catalyzed C-H chlorinaiton

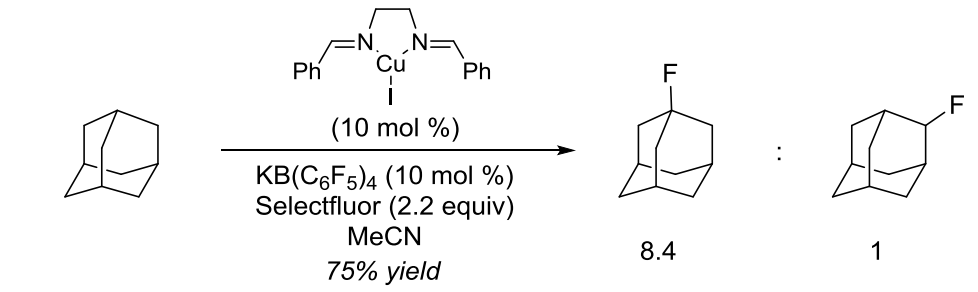


of alkyl bromide products as well. Most interestingly, Groves suggests that changing the identity of the meso subustituient on the porphyrin ligand changes the selectivity of the reaction. The results in Error! Reference source not found.**,** above, show that the more bulky tetramesetylporphyrin (TMP) catalyst directs the majority of chlorination to the β position, rather than the α position.[37] In 2012, Groves and coworkers expanded their method to an aliphatic C-H fluorination using AgF, TBAF as fluoride sources.[38]

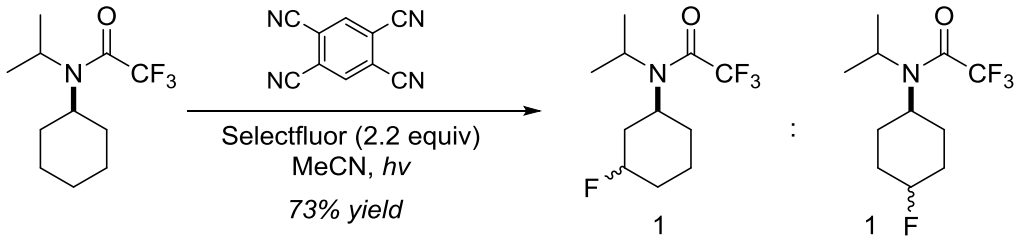
Installation of alkyl fluoride functionality is of great synthetic importance. Fluorine serves as a bioisostere for hydrogen; replacing a C-H bond with a C-F bond does not change a molecules bioactivity, but makes the molecule less sensitive to degradation at that position. Aliphatic fluorination presents a much different synthetic challenge than that of chlorination or bromination. Free radical fluorination with fluorine gas is an extremely exothermic and unselective reaction due to the low bond dissociation energy of F_2 (36.6 kcal/mol). The use of molecular fluorine can also result in C-C cleavage and unpredictable explosions.[39] The development of alternative electrophilic fluorine sources such as *N*-flurobenzenesulfonimide (NFSI) and Selectfluor® have greatly increased the synthetic accessibility of fluorination chemistry. The two sources of fluorine above have been shown to fluorinate carbon centered radicals with modest efficiency.[40] Therefore, generating a carbon centered radical from an alkane in the presence of an electrophilic fluorine source should prove a fruitful strategy for aliphatic fluorination.

Selectfluor® is a derivative of 1,4-diazabicyclo[2.2.2]octane that has been used extensively as the stoichiometric fluorine source for C-H fluorination by the Lectka group. Two such examples are shown below (**Figure 1-11**). Lectka shows two different strategies for generating carbon-centered radicals, which are fluorinated by Selectfluor. First, a copper complex is employed along with a tetrafluoroborate salt. Mechanistic studies revealed that the catalyst acts as an initiator in the reaction. A *N*-centered radical cation was identified as the abstracting species in the reaction. Thus, Selectfluor® is involved in both the C-H abstraction and fluorine atom delivery.[41,42] The second method uses tetracyanobenzene (TCB) as a photosensitizer that can directly oxidize the alkane substrate. TCB photooxidation has also been used to preform aliphatic C-H arylation reactions. Lectka and coworkers show that fluorination occurs at more electron-rich sites.[43]

Figure 1-11. Aliphatic fluorinations using Selectfluor®



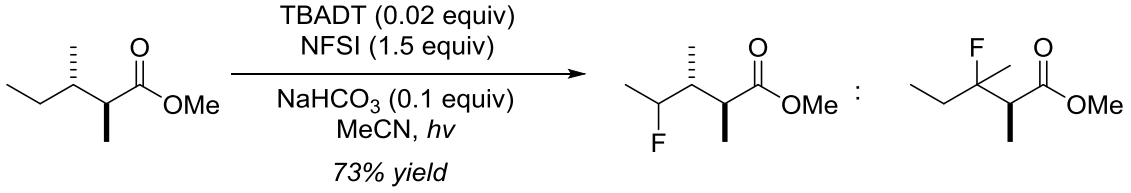
Lectka, *ACIE,* **2012,** 10580.



Lectka, *Chem. Sci.,,* **2014,** 1175.

Fluorosulfonimides are also competent sources of fluorine atoms. Britton reports aliphatic C-H fluorination using a polyoxotungstate complex and NFSI as the fluorine source (**Figure 1-12**). The reaction is a photocatalytic process and fluorinates a variety of alkane substrates including amino acid derivatives. The polyoxometylate system was extensively compared to Groves's Mn catalyzed system. The authors that similar reactivity and selectivity can be achaived through the use of their reaction conditions.[44]

Figure 1-12. Photocatalytic fluorination with a polyoxmetalate catalyst



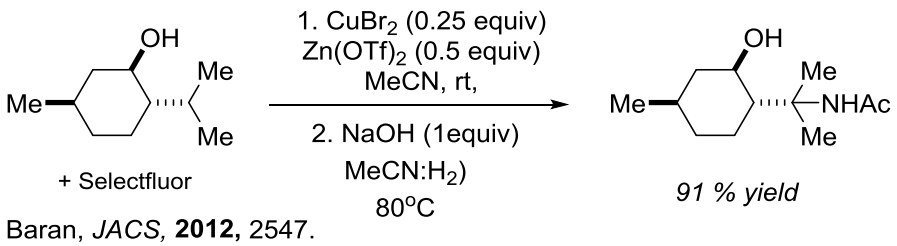
Britton, *ACIE,* **2014,** 4690.

1.2.3 Aliphatic C-H Amination

Intermolecular amination of unactivated aliphatic C-H bonds is by far the least developed class of C-H functionalization reactions discussed herein. Functional groups containing C-N bonds are extremely comment in biologically active molecules, many of which owe their activity to this polar group. As a result, the development of reactions that directly replace C-H bonds with C-N bonds has been an area of rapid development. Most of the methods, however, are *intra*molecular reactions, require the use of directing groups, or functionalize aryl sp^2 sites and will not be discussed here.

In 2012, Baran and coworkers presented one of the first synthetically practical C-H amination reactions of aliphatic sp^3 C-H bonds. The system developed is a mild, copper-catalyzed reaction tolerant of a variety of alkane and oxygenated alkane substrates. Baran and coworkers suggest that an unstable copper (III) – Selectfluor® complex may be responsible for the C-H abstratction, though they also suggest potential involvement by the nitrile solvent. Under the oxidizing conditions of the reaction, the carbon centered radical formed is oxidized to the carbocation and subsequently trapped by acetonitrile. Basic aqueous workup affords the C-H amination products. The authors suggest no detailed explanation for the origin of site selectivity in their reaction. In some examples reactivity is preferred at methylene sites instead of methine sites, so some steric component may be involved in the C-H abstraction event.[45]

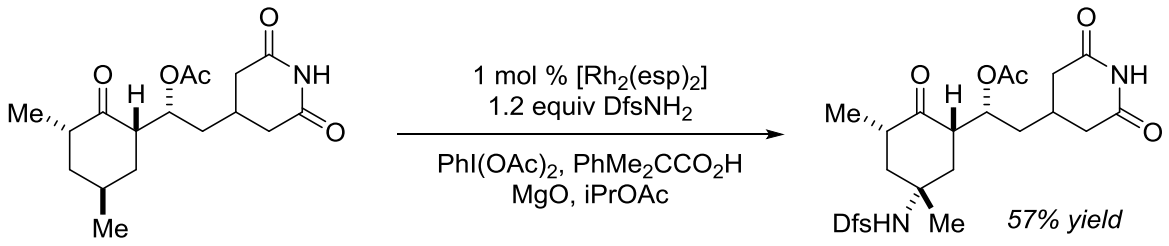
Figure 1-13. Ritter-type aliphatic C-H amination



Baran, *JACS,* **2012,** 2547.

The following year the Bu Bois group developed a C-H amination using a dirhodium tetracarboxylate catalyst [$Rh_2(esp)_2$]. The transformation selectively installs a substituted sulfamate at aliphatic tertiary C-H bonds in the substrate. The reaction is tolerant of both oxygen and nitrogen functionality. The reaction is believed to occur through a concerted nitrene insertion mechanism supported by kinetic isotope, radical clock, and enantiospecific insertion experiments. This chemistry developed by Du Bois is an excellent step toward practical aliphatic C-H amination but remains limited to reaction at methine sites. An expansion of this chemistry with the ability to react at methylene sites would be of high synthetic value.[46]

Figure 1-14. Intermolecular rhodium catalyzed C-H amination

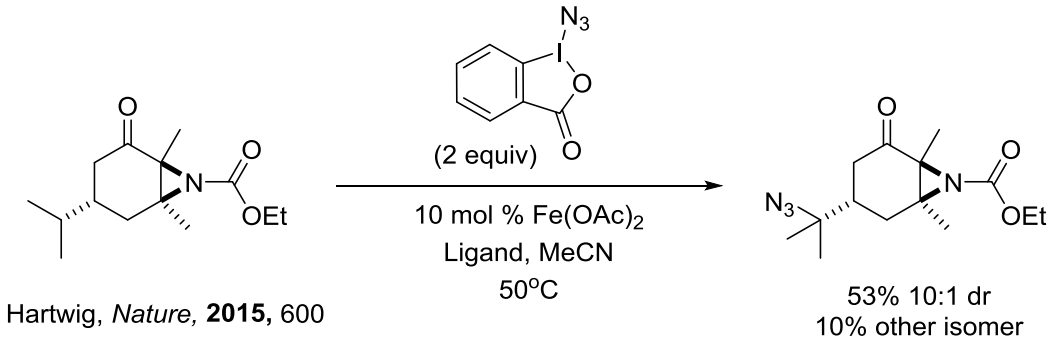


Du Bois, *Angew. Chem. Int. Ed.*, **2013**, 11343.

C-H azidation has also been targeted as a strategy for the efficient installation of nitrogen functionality. The azide is an attractive functional group because of the wide variety of different transformations it can undergo; azides can be converted to amines, amides, tetrazoles, triazoles and other heterocycles all under relatively mild reaction conditions. Recognizing this opportunity, Hartwig and coworkers developed an aliphatic C-H azidation reaction utilizing a unique hypervalent iodine azide reagent. The reaction relies on an $Fe(OAc)_2$ catalyst to proceed with reasonable efficiencies. The C-H azidation reaction, similar to the Du Bois' chemistry described above, heavily favors reaction at tertiary C-H bonds. The azidation reactions proceed with modest to excellent selectivity. The exact details of the reaction mechanism have not yet been uncovered,

though the authors propose that an iron species is likely involved in the C-H abstraction event to form a tertiary carbon centered radical. Steric and electronic effects may help differentiate between different tertiary sites within the molecule.[47]

Figure 1-15. Aliphatic C-H azidation with hypervalent iodine reagent



Hartwig, *Nature,* **2015,** 600

53% 10:1 dr
10% other isomer

1.3 Summary and Outlook

While there has been a wealth of development in the area of intermolecular aliphatic C-H functionalization in recent years, there is still significant need for development in terms of selectivity, reaction efficiency, and increased reaction types. Many traditional and even modern C-H functionalization methodologies still rely on the use of the alkane substrate as the solvent in the reaction. This may be useful in initial reactivity studies, but limiting the amount of substrate to 1 equivalent is required for complex molecule or late-stage applications. Additionally, an increased chemical understanding of the origin of site-selectivity in these reactions is required in order to ultimately improve or change selectivity. C-H oxidations, fluorinations, and aminations that meet this criteria have recently been developed. There still exists a need, however, for practical, efficient C-H bromination and chlorination protocols – particularly reactions that are selective for methylene sites in a molecule.

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2. CHAPTER TWO

Aliphatic C-H Bromination Using *N*-Bromoamides

2.1 Introduction

An important goal of modern chemical synthesis is to develop transformations that achieve site-selective intermolecular functionalization of aliphatic C-H bonds.[1] C-H Halogenation is a particularly attractive manifold due to the ability to convert alkyl bromides into a variety of other products. Aliphatic C-H bromination has long been used as a convenient method in the synthesis of alkyl bromide building blocks. Existing technologies to accomplish this goal often require large excess of alkane substrate, harsh reaction conditions, and give low yields of complex product mixtures.[2] This limits the synthetic utility of existing methods. Additionally, most free-radical bromination procedures select for the most labile C-H bonds present in the molecule: tertiary, benzylic or allylic C-H bonds. New methods are required to achieve complementary selectivity and reactivity efficient enough for late stage functionalization.

2.2 Background

Alkane bromination was one of the first C-H functionalization methods reported, though little work has been done since to improve on the initial methods. Alkane bromination is the conversion of an aliphatic sp^3 C-H bond into a C-Br bond resulting in an alkyl bromide product. See **Chapter 1.2.2** for an overview of alkane bromination methods.

2.3 Reaction Development

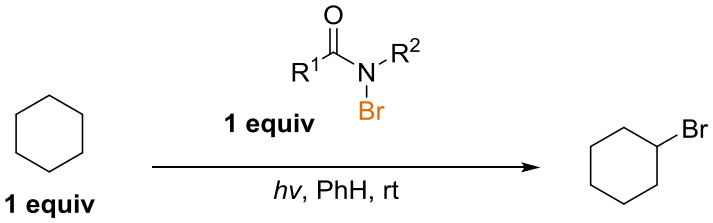
Hofmann-Löffler-Freytag processes use nitrogen-centered radicals to perform site-selective, intramolecular C−H functionalizations, including C−H halogenations. These processes capitalize on the kinetic preference for 1,5-H-atom abstraction by heteroatom-centered radicals to achieve near single-site selectivities. Intermolecular, heteroatom-centered radical-mediated functionalizations of unactivated aliphatic C−H bonds, are rarely used in synthesis due to low selectivities.[3] Interestingly, preliminary reports by Minisci and Deno (discussed in **Chapter 1)** indicate that site-selective, intermolecular C−H functionalizations using N-centered radicals may be possible. A number of factors limit their synthetic utility: (1) the use of strong acid as solvent (2) alkane substrate as co-solvent.[4] We hypothesized that the development of a set of simple, stable reagents that deliver an array of unique N-centered radicals could enable a new approach to site-selective, intermolecular C−H halogenation. Tuning the steric and electronic parameters of the reacting species enables reagent-controlled C−H halogenations that override inherent substrate-controlled selectivities.

2.3.1 Initial Studies

Inspired by initial reports that *N*-haloamide reagents can affect C-H halogenation without the use of strong acid, we pursued a synthetically useful intermolecular C−H bromination using N-bromoamides. Initially, we pursued the C−H bromination of simple cycloalkanes with substrate as limiting reagent. While there are reports of aliphatic C−H bromination using excess alkane substrate,[5] the only studies with substrate as limiting reagent that proceed with practical yields (i.e., >50%) require highly reactive superacids and are not suitable for general applications in synthesis.[6] We began with the bromination of cyclohexane (1 equiv) using a number of N-bromoamide reagents (**Table 2-1**). These N-bromoamides are stable solids that are easily accessed

from their parent amides.[7] While all of the bromoamides examined provided cycloalkyl bromide product, hindered electrophilic reagents proceeded with improved efficiency (**Table 2-1,** Entry 5 and 6). *N*-bromoamide 6 provided cyclohexyl bromide in the highest yield of the reagents studied (70%, entry 6). Notably, these experiments were performed on the benchtop at room temperature with common 100W household bulbs (23W fluorescent bulbs provided equivalent yields) and are complete in <30 min. While we typically perform these reactions under Ar using purified reagents

Table 2-1. Bromination of cyclohexane with various *N*-bromoamides[a]



entry	reagent	% yield
1	**1**: R^1 = Ph; R^2 = H	25
2	**2**: R^1 = Ph; R^2 = *t*Bu	44
3	**3**: R^1 = Ph; R^2 = CH_2CF_3	52
4	**4**: R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = CH_2CF_3	57
5	**5**: R^1 = *p*-$NO_2C_6H_4$; R^2 = *t*Bu	65
6	**6**, R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu	70
7	**6**, R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu	68[b]

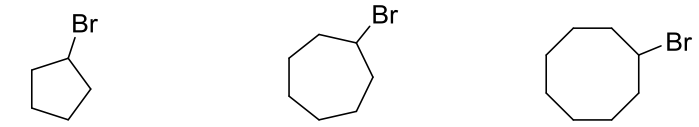
[a]Reactions were performed in PhH at rt under Ar using visible light irradiation with 1 equiv of substrate and N-bromoamide. Yields were determined by GC analysis.
[b]Reaction performed under air atmosphere using commercial, unpurified reagents.

and solvents; there is only a minor decrease in yield when the reaction is run in air with undistilled reagent-grade chemicals (**Table 2-1**, entry 7). Stoichiometric reactions with other cyclic hydrocarbons proceeded with similar efficiencies. Dihalogenation was not observed in any

appreciable amounts in these reactions. We attribute this to the electronic deactivation of the bromoalkane products.

Other cycloalkanes also performed favorable in the reaction using *N*-bromoamide 6. Cyclopentane, cycloheptane, and cyclooctane all gave good yields of the corresponding bromide products. The slightly lower yield when using cyclopentane can be attributed to the volatility of the substrate (**Figure 2-1**).

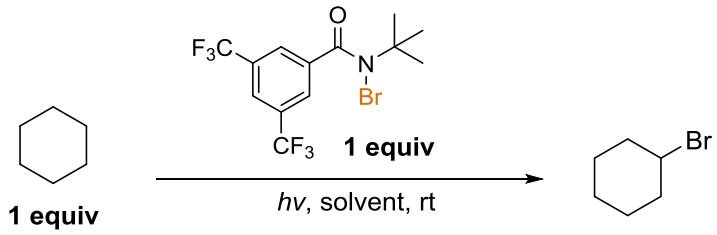
Figure 2-1. Bromination of additional cycloalkanes with *N*-bromoamide 6



54% yield 72% yield 75% yield

Benzene was chosen as the solvent for the reaction because it contains no aliphatic sp^3 C-H bonds. Therefore, it is unlikely that the solvent will compete with the substrate for bromination. While this hypothesis held true, we tested a number of different solvents to see if any gave improved reactivity or were equally amenable to the reaction conditions. A selection of the solvents screened are shown in (**Figure 2-2).** Chlorinated alkane solvents (**Figure 2-2**, entry 1, 2 and 3) gave modest yields. Diminished yields in chloroalkane solvents likely results from competitive solvent bromination. The reaction is not amenable to polar amine solvents (MeCN) or polar protic solvents (MeOH). A number of aromatic solvents were also screened. Electrophilic radicals are known to complex to aromatic systems, so we hypothesized such complexation might have some impact on the efficiency of the reaction.[8] All aromatic solvents, however, performed with similar efficiencies (Figure 2-2, entries 4, 5, and 7). With optimized reaction conditions in hand we set out to explore the selectivity of the system with a variety of alkane substrates.

Figure 2-2. Bromination of cyclohexane in various solvents



entry	solvent	% yield
1	CH_2Cl_2	25
2	$CHCl_3$	29
3	DCE	30
4	$PhCF_3$	62
5	PhCl	61
6	MeCN	NR
7	PhH	70

[a]Reactions were performed at rt under Ar using visible light irradiation with 1 equiv of substrate and N-bromoamide. Yields were determined by GC analysis.

2.3.2 Substrate Scope – Steric Selectivity

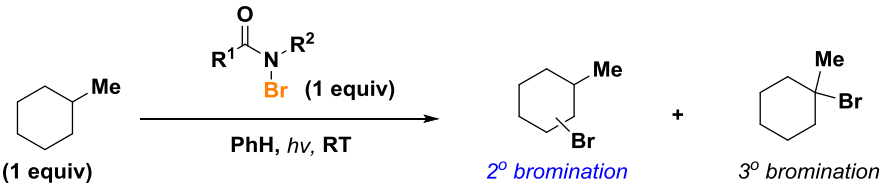
We next explored the potential for site-selective C−H functionalization. The ability to differentiate sites of functionalization on both steric and electronic bases is paramount. Classical radical-mediated C−H brominations are often selective for tertiary C−H sites as discussed previously.[9] In addition, the preference for tertiary C−H functionalization is also characteristic of the majority of known polar or metal-catalyzed C−H functionalizations.[10] We hypothesized that tuning the steric and electronic parameters of the bromoamide involved in our system could offer the potential to overcome this inherent reactivity profile.

We began with the selective functionalization of methylcyclohexane to survey the selectivity of secondary (desired) versus tertiary (undesired) C−H functionalization (**Table 2-2**).

The bromination of methylcyclohexane using common reagent N-bromosuccinimide (NBS, **Table 2-2,** entry 7) requires a large excess of substrate to deliver greater than a trace amount of product, and therefore was performed neat in methylcyclohexane. As expected, this reaction greatly favored halogenation at the tertiary C−H site after correcting for the number of tertiary (1) and secondary (10) sites available ($k_{secondary}/k_{tertiary}$, k_s/k_t, = 0.06). Bromination using a biomimetic Mn-porphyrin system (**Table 2-2,** entry 8) also favored tertiary halogenation (k_s/k_t, = 0.40). The photochemical C−H bromination using bromoamide 1 proceeded with a k_s/k_t selectivity comparable to NBS (0.07, **Table 2-2,** entry 1), while the reactions of N-bromoamides 3 and 4 were comparable to the Mn-porphyrin system (**Table 2-2,** entries 5 and 6). However, the use of bulky N-tBu reagents 2, 5, and 6 led to a marked increase for methylene functionalization, with bromoimide 6 providing >98% selectivity and k_s/k_t = 6.6 (**Table 2-2,** entry 6). This level of methylene selectivity in the functionalization of a simple cyclic hydrocarbon is unmatched by any known system for aliphatic C−H halogenation.

A particularly intriguing aspect of these results is the ability to alter the site selectivity through changing the N-substituent of the reagent used. While N−H and N-trifluoroethyl *N*-bromoamides 1, 3, and 4 favor functionalization of the weakest C−H bond (tertiary), *N*-tBu reagents 2, 5 and 6 strongly favor functionalization at the less sterically hindered secondary sites. The ability to overcome inherent substrate dictated selectivity in intermolecular, aliphatic C−H functionalization is a notable goal,[11] and the use of easily tuned bromoamides such as those presented herein offers an attractive solution to this problem.

Table 2-2. Bromination of methylcyclohexane



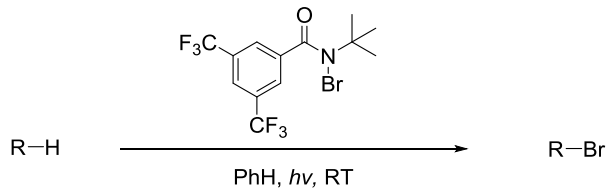
entry	reagents	% 2° Br	% 3° Br	$k_{secondary}/k_{tertiary}$	
1	**1**: R^1 = Ph; R^2 = H	40.2	59.8	0.07	
2	**2**: R^1 = Ph; R^2 = *t*Bu	98.1	1.9	5.2	
3	**3**: R^1 = Ph; R^2 = CH_2CF_3	77.6	22.4	0.35	
4	**4**: R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = CH_2CF_3	79.8	20.2	0.40	
5	**5**: R^1 = *p*-$NO_2C_6H_4$; R^2 = *t*Bu	98.3	1.7	5.8	
6	**6**, R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu	**98.5**	**1.5**	**6.6**	**(75% yield)**
7	NBS, AIBN (neat)	37.8	62.2	0.06	
8	Mn(TPP)Cl/NaOBr	79.8	20.2	0.40	

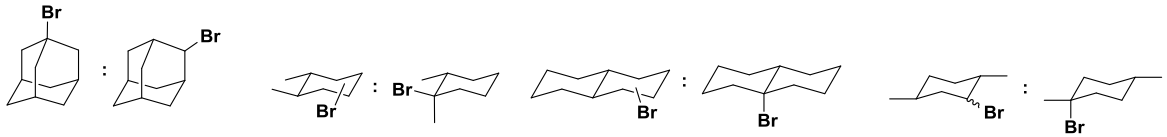
[a]Reactions were performed in PhH at rt under Ar using visible light irradiation with 1 equiv of substrate and N-bromoamide. Yields were determined by GC analysis.

Examination of the steric-based selectivity of our approach continued with a number of hydrocarbon substrates used as benchmarks for site-selective aliphatic C−H functionalization (**Table 2-3**). In each case, the C−H bromination proceeded with excellent levels of steric selectivity. The bromination of norbornane occurs exclusively on the *exo*-face of the bicyclo[2.2.1]heptane framework (**Table 2-3,** entry 5). The functionalization of trans-1,2-dimethylcyclohexane proceeds only at the methylene sites (**Table 2-3,** entry 2). The more challenging cis-1,2- dimethylcyclohexane contains a relatively unhindered tertiary equatorial C−H bond that is prone to react owing to the release of 1,3-diaxial strain.[12] Using bromoimide 6, the bromination remains selective for the methylene positions of the carbocycle (ks/kt = 3.0, **Table 2-3,** entry 6). This remarkable level of methylene selectivity of aliphatic C−H halogenation with this substrate is higher than any other C−H functionalization method previously reported.[13]

The halogenation of adamantane proceeds with modest site selectivity with common radical halogenating agents (e.g., Br_2 and NBS), yet favors the less encumbered tertiary sites with sterically selective reagents.[14] The reaction of adamantane with N-bromoamide 6 was highly selective for the tertiary site (kt/ks >100), consistent with previous studies of amidyl radical selectivity (**Table 2-3,** entry 1).[4c] The bromination of trans-decalin proceeds with excellent methylene site selectivity using 6 (>99%, **Table 2-3,** entry 3). *Cis*-Decalin is a more challenging

Table 2-3. Sterically selective bromination of diverse hydrocarbon substrates[a]



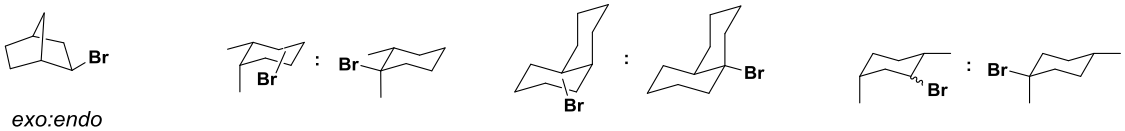


(36:1) 58% yield
adamantane
(1)

(>99:1) 53% yield
1,2-trans dimethyl cyclohexane
(2)

(>99:1) 45% yield
trans-decalin
(3)

(>99:1) 57% yield
1,4-trans dimethyl cyclohexane
(4)



exo:endo
(>99:1) 63%
norbornane
(5)

(12:1) 50% yield
1,2-cis dimethyl cyclohexane
(6)

(>99:1) 55% yield
cis-decalin
(7)

(15:1) 51% yield
1,4-cis dimethyl cyclohexane
(8)

[a]Reactions were performed in PhH at rt under Ar using visible light irradiation with 1 equiv of substrate and N-bromoamide. Yields were determined by GC analysis.

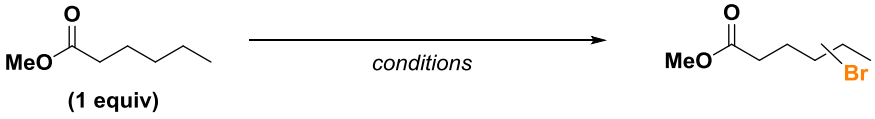
substrate for methylene-selective functionalization, and only modest 2°/3° selectivity has been achieved to date, owing to the presence of a reactive equatorial 3° C−H bond.[15] With reagent 6, the bromination of cis-decalin is also highly selective for methylene functionalization (>99%,

Table 2-3, entry 7), further demonstrating the unique levels of steric selectivities obtained using our system.

2.3.3 Substrate Scope- Electronic Selectivity

Next we surveyed the potential for electronic site selectivity in the C−H halogenation using methyl hexanoate as a test substrate (**Table 2-4**). The Mn-porphyrin-catalyzed bromination[5a] of this substrate is highly selective for the δ and γ sites, although there is little discrimination between these two positions (**Table 2-4,** entry 2). Functionalization using N haloamide 6 (2 equiv) leads to a δ- selective process, favoring functionalization of the methylene position furthest removed from the electron-withdrawing ester group (**Table 2-4,** entry 1). We also observe γ-functionalization, but bromination with reagent 6 provides good selectivity between the δ and γ sites (δ:γ = 3.2:1).

Table 2-4. Bromination of methylhexanoate[a]



(1 equiv)

		bromoalkane isomer distribution (%) α β γ δ ω					
entry	conditions	MeO_2C—CH_2—CH_2—CH_2—CH_2—CH_3					
1	bromoamide **6 (2 equiv),** PhH, *hv,* RT	5.2	10.1	18.1	58.8	7.8	**(56% yield)**
2	Mn(TPP)Cl, NaOBr	---	7.7	44.2	45.7	3.1	
3	Br_2, CH_2Cl_2, *hv,* RT	21.6	8.8	18.8	50.4	1.1	
3	NBS, CH_2Cl_2, *hv,* RT	17.9	10.7	20.5	47.9	3.1	

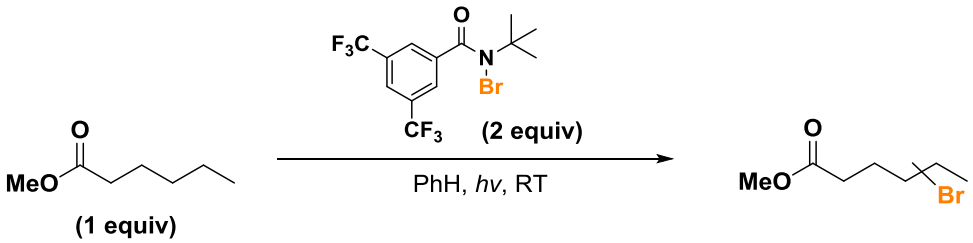
[a]Reactions were performed at rt under Ar using visible light irradiation with 1 equiv of substrate and N-bromoamide or other brominating agent. Yields were determined by GC analysis.

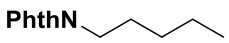
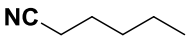
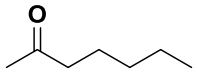
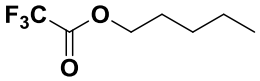
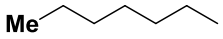
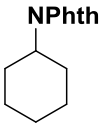
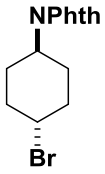
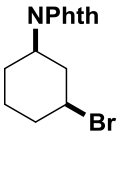
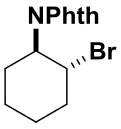
Our studies of electronic selectivity continued with a set of linear functionalized hydrocarbons as substrates (**Table 2-5**, entries 1−5). The functionalization of phthalimide-protected pentylamine using reagent 6 proceeded with even greater site selectivity than methyl hexanoate, with a remarkable 81.8% selectivity for the δ site (**Table 2-5,** entry 1). No α or β

functionalization was observed, clearly indicating the excellent potential for electronically dictated site selectivity using protected primary amines. The functionalizations of both hexanenitrile and heptan-2-one also proceeded with good δ selectivities (68.3% and 53.8%,respectively, **Table 2-5** entries 2 and 3). The promising level of δ selectivity with heptan-2-one is intriguing given the known protocols for the α-halogenation of ketones using simple brominating agents (e.g.,NBS) and visible light.[16] The reaction of pentyl trifluoroacetate also displayed good δ selectivity (66.6%, **Table 2-5,** entry 4). Bromination of n-hexane was 58.7% δ selective, indicating the possibility of a minor steric component in reactions of linear substrates (**Table 2-5,** entry5). A minor amount of dihalogenation of n-hexane was observed; therefore, a reaction using an excess of substrate was performed to determine the site selectivity. While further studies will seek reagents with improved selectivities, the efficiency of these reactions already positions this method as a practical (>50% yield) approach to C−H bromination.

We also examined the site selectivity using a functionalized cycloalkane substrate, phthalimide-protected cyclohexylamine (**Table 2-5,** entry 6). The C−H bromination favored reaction at the C3 and C4 positions (91.5%), with only a minor amount (8.5%) of the C2 product detected. The C3 bromination delivered the 1,3-cis product as a single diastereomer, and the C4 bromination proceeded diastereoselectively to yield two products with a 80:20 dr favoring functionalization trans to the phthalimide group. The potential for diastereoselective methylene C−H halogenation is intriguing and is a useful complement to C−H oxidation approaches which typically deliver sp2-hybridized ketone products at methylene sites.

Table 2-5. Electronically selective bromination of functionalized hydrocarbons[a]



entry	substrate	% selectivity of bromination α β γ δ ω EWG—CH_2—CH_2—CH_2—CH_2—CH_3	combined yield (%)
1		— — 5.6 81.8 11.7	**56**
2		3.2 2.7 11.6 68.3 14.2	**50**
3		13.3 8.3 16.2 53.8 8.4	**72**
4		— 3.6 13.4 66.6 16.4	**73**
5		— — 30.1 58.7 11.2	**66**
6		 46.1 dr=80:20	 45.4 dr>95:5	 8.5 dr>95:5	**61**

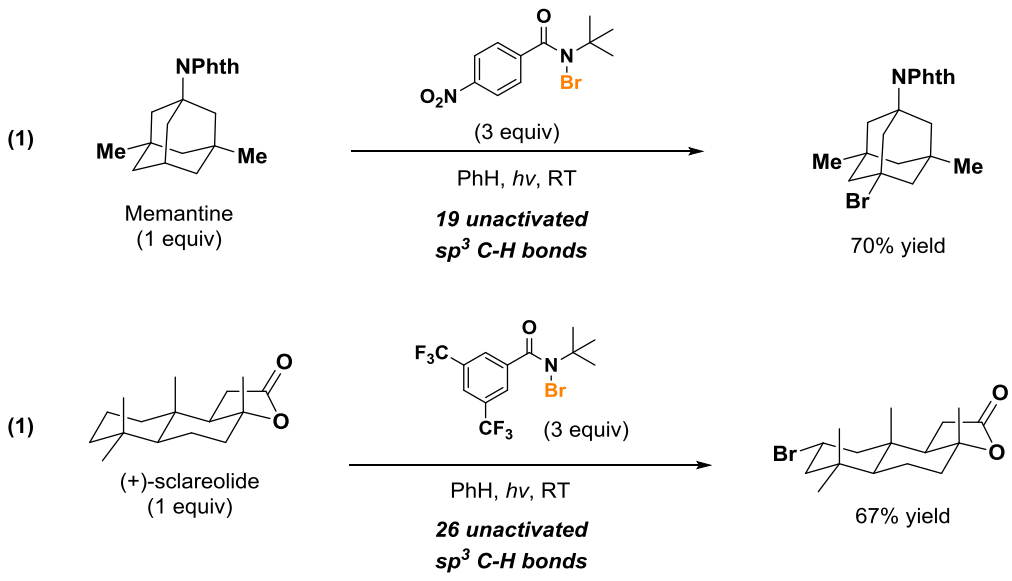
[a]Reactions were performed in PhH at rt under Ar using visible light irradiation with 1 equiv of substrate and 2 equiv N-bromoamide. Yields were determined by GC analysis.

2.3.4 Substrate Scope – Complex Molecules

We have also begun an initial survey of more complex substrates (**Figure 2-3**). Amino-adamantanes are found in a large number of pharmaceuticals, typified by the anti-Alzheimer's drug Namenda. The functionalization of the adamantane core is usually achieved via electrophilic bromination using excess bromine (~10 equiv).[17] This strategy has not been successful using

nitrogen- or oxygen-substituted adamantanes; the simple electrophilic halogenation of amino-adamantanes is unknown. The site-selective C−H bromination using N-bromoamides proved to be an excellent solution. Functionalization of the *N*-phthalimide derivative of memantine (**Figure 2-3,** entry 1) using N-bromoamide 5 delivered tertiary bromination product in good isolated yield (70%), with complete site selectivity. As observed in the reaction of adamantane, the amidyl radical favors C−H abstraction at the less-hindered tertiary C−H site.

Figure 2-3. Bromination of drug-like molecules



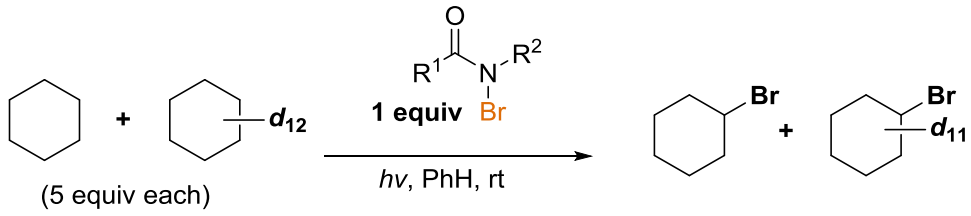
The terpenoid natural product (+)−sclareolide (**Figure 2-3,** entry 2) contains 26 aliphatic C−H bonds, with diverse steric and electronic control elements, and has recently been studied using a number of C−H functionalization methods.[4a,5a,5d,6] The functionalization of (+)-sclareolide using reagent 6 under visible light irradiation at room temperature provides the C2-equatorial bromination product in 67% isolated yield as a single regio- and stereoisomer. Notably, as with all C−H brominations reported herein, the substrate is the limiting reagent, and no recycling of unreacted starting material is required. For comparison, the only other reported C−H bromination

of (+)-sclareolide involves a large excess of substrate and proceeds with <5% conversion to a mixture of brominated derivatives.[5d]

2.3.5 Mechanistic Studies and Proposed Mechanism

In order to gain insight regarding the mechanism of the C−H halogenation we carried out a competitive kinetic isotope effect experiment between cyclohexane and d_{12}- cyclohexane using reagent 6. We observed primary kinetic isotope effect (KIE) of $k_H/k_D = 5.8$ (**Table 2-6**). This KIE approaches the theoretical maximum for primary KIE values. This value is consistent with an irreversible hydrogen atom abstraction. Based on the magnitude of the value we predict and even degree of C-H bond breakage and H-N bond formation during the transition state. We also wanted to probe the KIE with respect to the other *N*-bromoimide reagents synthesized. Each reagent possessed a unique KIE value (values represent the averages of multiple experiments). The KIE

Table 2-6. Kinetic isotope effect of varying *N*-bromoamide reagents[a]



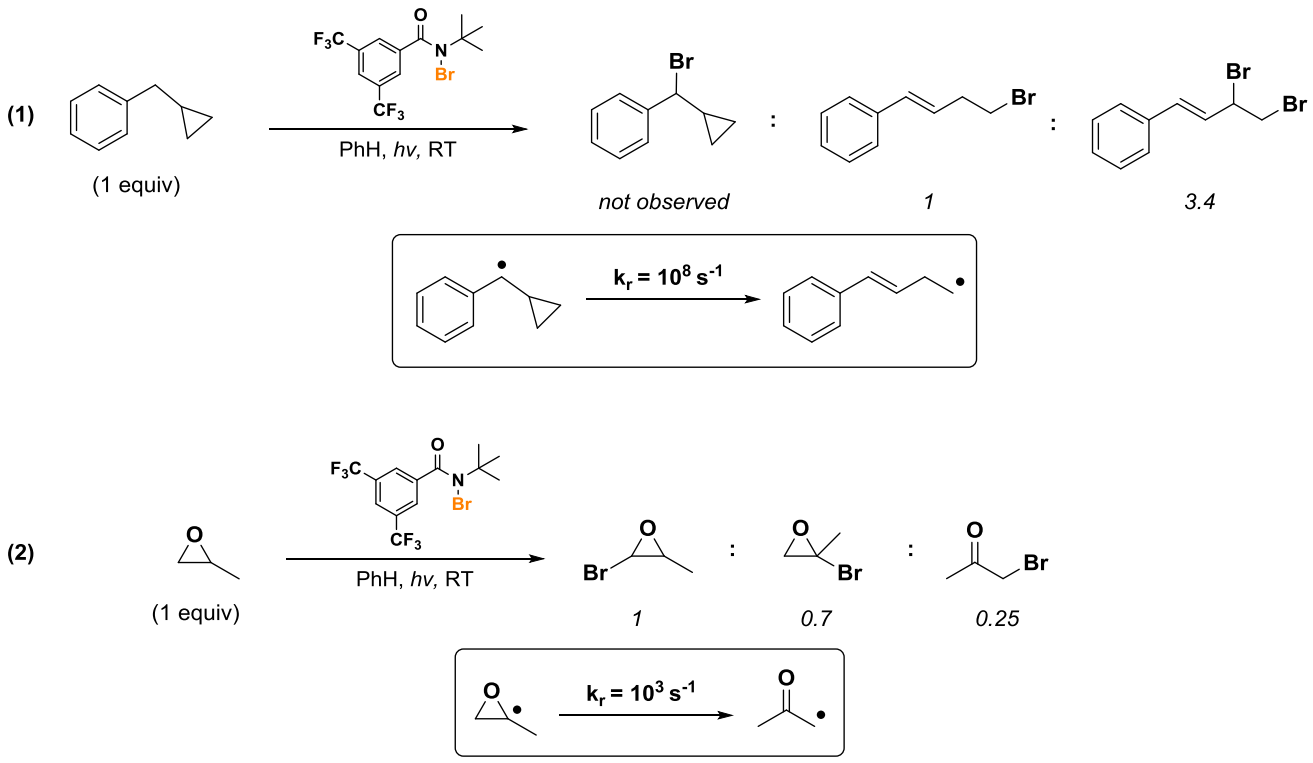
entry	reagent	k_H/k_D
1	**1**: R^1 = Ph; R^2 = H	2.2
2	**2**: R^1 = Ph; R^2 = *t*Bu	5.7
3	**3**: R^1 = Ph; R^2 = CH_2CF_3	4.8
4	**4**: R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = CH_2CF_3	3.3
5	**5**: R^1 = *p*-$NO_2C_6H_4$; R^2 = *t*Bu	5.1
6	**6**, R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu	5.8

[a]Reactions were performed in PhH at rt under Ar using visible light irradiation with 5 equiv of substrate and 1 equiv N-bromoamide. Yields were determined by GC/MS analysis.

values range from k_H/k_D = 2.2-5.8, with all reagents exhibiting a large primary KIE. This data is consistent with a similar mechanism for each reagent, but differing C-H abstracting species. Therefore, each unique amidyl radical generated, possessed its own unique reactivity. Under identical conditions, neither Br_2 nor N-bromosuccinimide delivered more than a trace amount of product. This is again consistent with an amidyl radical C−H abstraction step in our approach, as further supported by the site selectivity studies discussed above.

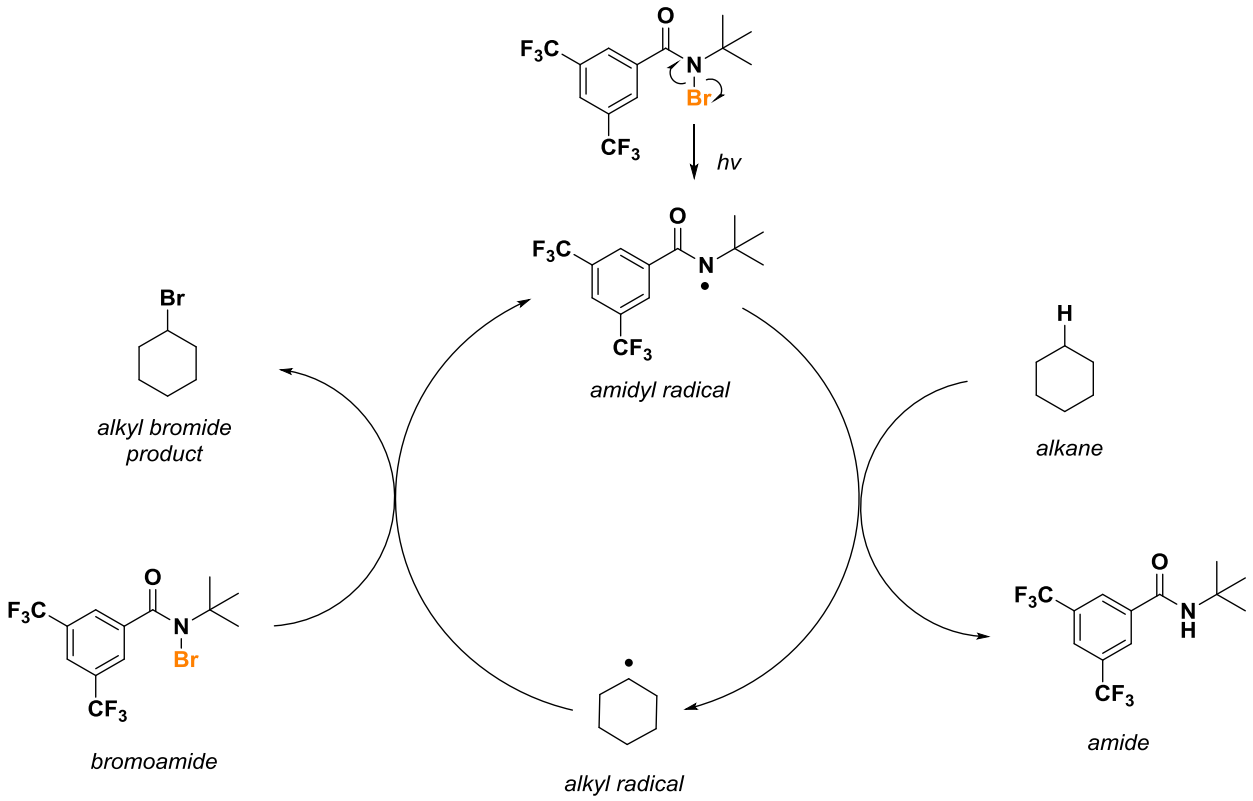
Next we set out to probe the radical nature of the mechanism. We hypothesized that an amidyl radial is the key C-H abstracting species in our reaction, but also that carbon centered radicals are generated throughout the process. Radical clock substrates are a key mechanistic probe for determining the presence of carbon centered radicals.[18] We subjected a number of different alkane substrates that we envisioned could function as radical clocks to the standard reaction conditions; two of those substrates are shown in **Figure 2-4**. Benzyl cyclopropane (**Figure 2-4**, equation 1) was subjected to the standard reaction conditions. To ring opening products were observed, while no cyclopropane starting material was observed. This suggests the presence of a carbon centered radical in the mechanism. Propylene oxide was also subjected to the same reaction conditions (**Figure 2-4**, equation 2). The radical rearrangement of propylene oxide occurs on a timescale five orders of magnitude slower than in the previous example. We observed bromination of the substrated itself as well as rearranged products. This further supports the presence of a radical process, but also points to a somewhat long-lived carbon-centered radical intermediate in the mechanism.

Figure 2-4. Radical clock experiments with *N*-bromoamide 6



We incorporated the experimental data above into a more complete mechanistic proposal for our C-H bromination reaction (**Figure 2-5**). We hypothesize that when subjected to visible light irradiation the weak N-Br bond homolytically cleaves to give an amidyl radical. The putative amidyl radical then abstracts an H-atom from a molecule of alkane substrate to form a molecule of amide and a carbon centered radical. The amide becomes a spectator in the reaction, while the carbon centered radical can abstract a bromine atom from another molecule of *N*-bromoamide reagent. This final step yields a molecule of alkyl bromide product and another molecule of amidyl radical, which propagates the radical-chain mechanism. Our proposal is consistent with the experimental data described above; additionally the presence of an *N*-centered radical as the abstracting agent is consistent with previous C-H halogenation studies (see **Chapter 1).**

Figure 2-5. Proposed mechanism for aliphatic C-H bromination with *N*-bromoamides

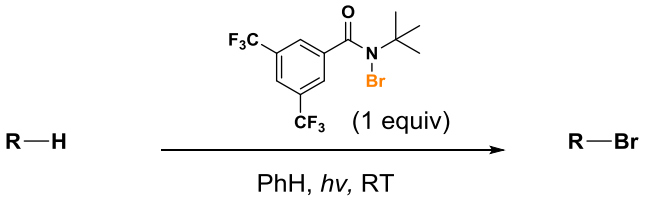


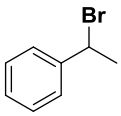
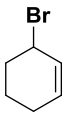
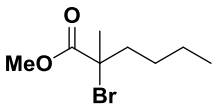
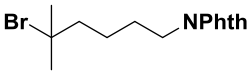
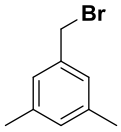
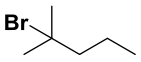
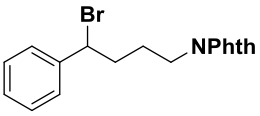
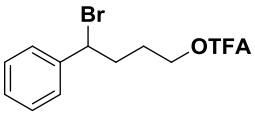
2.3.6 Substrate Scope – Bromination of activated C-H bonds

The main goal of the C-H bromination described above is to selectively functionalize aliphatic sp^3 C-H bonds. We have demonstrated a number of bromoimide reagents so achieve this goal on a variety of alkane substrates. We also were intrigued at the ability of our reagent to stand up to traditional benzylic and allylic bromination protocols like the Wohl-Zeigler reaction.[19] Traditional methods for benzylic, allylic and tertiary bromination can be synthetically laborious, often requiring multiple equivalents of radical initiator and NBS, long reaction times, and toxic solvents (carbon tetrachloride). Aliphatic tertiary bromination generally requires multiple equivalents of alkane. In light of these drawbacks we subjected a number of alkane substrates

containing allylic, benzylic and acyclic tertiary C-H bonds to our reaction conditions. We found that in each case the reaction proceeds in good yield, with 1 equivalent of substrate and bromoimide after only short reaction times (**Table 2-7**). It is notable that in the presence of multiple activated C-H bonds, only mono-bromination occurs (**Table 2-7**, entry 2 and 5). The reactivity achieved here occurs with efficiency that cannot be achieved with NBS or Br_2.

Table 2-7. Bromination of activated C-H bonds using *N*-bromoamides[a]



			
95% yield	**67% yield**	**48% yield** (89% of pdt distribution)	**53% yield**
(1)	(2)	(3)	(4)
			
61% yield	**48% yield** (70% of pdt distribution)	**88% yield**	**72% yield**
(5)	(6)	(7)	(8)

[a]Reactions were performed in PhH at rt under Ar using visible light irradiation with 5 equiv of substrate and 1 equiv N-bromoamide. Yields were determined by GC or NMR analysis.

2.4 Summary

In conclusion, we have developed a site-selective, intermolecular bromination of unactivated, aliphatic C−H bonds using N-bromoamides and visible light. The high efficiency of this radical-mediated process permits the use of hydrocarbon as limiting reagent in all examples, which is critical to future applications in complex synthesis. These reactions proceed with site

selectivities that rival the most selective intermolecular C−H functionalizations known. Expansions of this approach to site selective C−H functionalization to other classes of small molecules and synthetic transformations are currently underway, with the ultimate goal of developing a set of easily accessed reagents capable of practical, predictable, and site-selective C−H functionalizations by way of tuned heteroatom-centered radicals.

2.5 Experimental Data

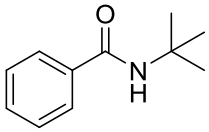
2.5.1 General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. GC Spectra were obtained using a Shimadzu GC-2010 gas chromatograph with a Shimadzu AOC-20s Autosampler, and Shimadzu SHRXI-5MS GC column. The results of the kinetic isotope study were analyzed using an Agilent Gas Chromatograph- Mass Spectrometer with a 6850 series GC system and a 5973 Network Mass Selective Detector. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400, DRX 500, or a Bruker AVANCE III 600 CryoProbe (^{1}H NMR at 400, 500 or 600 MHz and ^{13}C NMR at 100, 126 or 151 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.28 ppm, C_6D_6 at 7.16 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, tdd = triplet of doublet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained using an Agilent – LC-QTOF 6520: Accurate – Mass QTOF LCMS, 1200 series LC. Elemental Analysis was preformed by Robertson

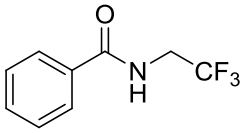
Microlit Laboratories in Ledgewood, NJ. Thin layer chromatography (TLC) was performed on SiliaPlate 250μm thick silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

2.5.2 Compound Preparation

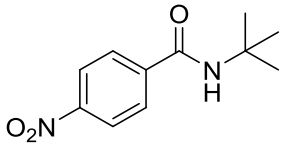
Amide Synthesis



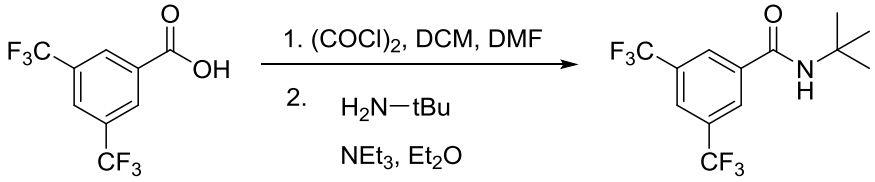
***N*-(*tert*-butyl)benzamide** was synthesized according to literature procedures[20] and purified via single solvent recrystallization from benzene. Physical and spectral data were in accordance with literature data.[21]



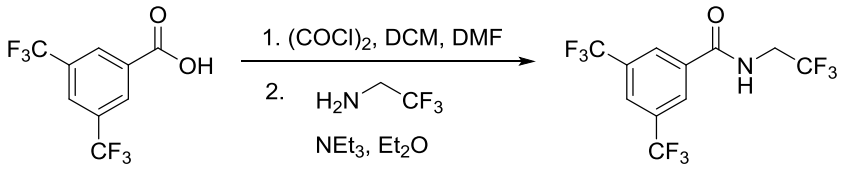
***N*-(2,2,2-trifluoroethyl)benzamide** was synthesized according to literature procedures and purified via single solvent recrystallization from pentane. Physical and spectral data were in accordance with literature data.[22]



***N*-(tert-butyl)-4-nitrobenzamide** was synthesized according to literature procedures[1] and purified via single solvent recrystallization from benzene. Physical and spectral data were in accordance with literature data.[23]



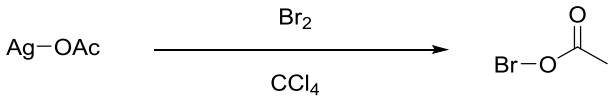
***N*-(tert-butyl)-3,5-bis(trifluoromethyl)benzamide** was synthesized by reacting tert-butylamine with the corresponding acid chloride in THF. To a 0 ºC solution of 10.0g carboxylic acid (38.75 mmol) in DCM (150 mL) and DMF (100 uL) was added 6.5 mL oxalyl chloride (71.50 mmol) dropwise under an argon atmosphere. The solution was stirred at 0 ºC for 15 min. then warmed to room temperature for 1.5 hours. The resultant solution was evaporated almost to dryness under reduced pressure to remove the DCM. The reaction mixture was dissolved in dry THF and cooled to 0 °C. Then 10.1 mL of tertbutylamine (71.5 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The reaction was diluted with Et_2O, washed with a 2.5M NaOH solution, 3x 1M HCl solution, 1x Brine, dried with magnesium sulfate and concentrated under reduced pressure. The product was purified via single solvent recrystallization from benzene to give the product (11.1 g, 35.5 mmol, 92% yield) as a white crystalline solid. Physical and spectral data were in accordance with literature data.[24]



To a 0 ºC solution of 3,5-bis(trifluoromethyl)benzoic acid (2.50 g, 9.61 mmol) in DCM (24 mL) and DMF (10 drops) was added oxalyl chloride (1.65 mL, 19.2 mmol) dropwise under an argon atmosphere. The solution was stirred at 0 ºC for 15 min then warmed to room temperature for 1.5 hours. The resultant yellow solution was evaporated to near dryness under reduced pressure to remove the DCM. The reaction mixture was dissolved in dry Et_2O and cooled to 0 °C. Triethylamine (1.0 mL, 10.1 mmol) and trifluoroethylamine (0.780 mL, 10.1 mmol) were added simultaneously, dropwise. The solution was allowed to warm to room temperature and stirred overnight. The ammonium salts were filtered using vacuum filtration and washed with Et_2O. The organic filtrate was concentrated under reduced pressure to give the crude product which was recrystallized from pentane to give *N*-(2,2,2-trifluoroethyl)-3,5-bis(trifluoromethyl)benzamide (2.9 g, 17.3 mmol, 90% yield) as a white solid.

Analytical data for ***N*-(2,2,2-trifluoroethyl)-3,5-bis(trifluoromethyl)benzamide**: **^{1}H NMR** (400MHz ,CHLOROFORM-d) δ = 8.27 (s, 2 H), 8.09 (s, 1 H), 6.52 (br s, 1 H), 4.24-4.16 (m, 2 H); **^{13}C NMR** (100MHz ,CHLOROFORM-d) δ = 164.7, 135.2, 132.9, 132.7, 132.5, 132.2, 127.5, 125.9, 125.8, 125.7, 125.5, 124.8, 123.6, 122.9, 121.8, 41.7, 41.5, 41.2, 41.0 ppm; **IR** (thin film, cm^{-1}) 3333.1, 3000.4, 2962.4, 1689.1, 1528.1, 1357.2, 1280.9, 1112.2, 909.3, 844.6, 702.6; **HRMS** (ESI) Calcd. for $[C_{11}H_6F_9NO+H]^+$ = 340.03, Found = 339.91

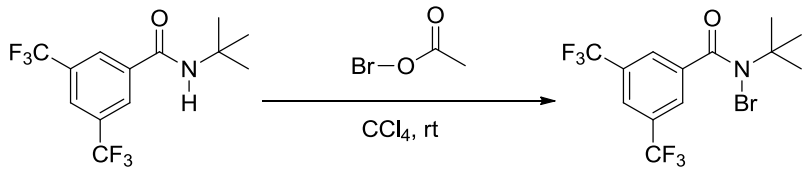
Acetyl Hypobromite



The general procedure for the preparation of acetyl hypobromite was based on the method reported by Beebe and Wolfe.[25] Carbon tetrachloride (105 mL) was freshly distilled into a flame-dreid flask and back filled with N_2 - 5 mL was removed for future use. The flask was then wrapped in foil and silver acetate (3.30g , 20 mmol) was added. The resultant suspension was then cooled to 0 °C and elemental bromine (1.05 mL, 20 mmol) was added dropwise. The reaction mixture was then stirred in the dark for an additional 15 min at 0 °C followed by quickly filtering into a separate, foil wrapped, flame-dried flask with limited suction to remove the silver bromide formed in the reaction. The collected silver bromide was then washed with 2-3 mL of distilled CCl_4. The collected orange solution was stored wrapped in foil at -10 °C and can be used with minimal decrease in concentration for 5 – 10 days. The concentration of acetyl hypobromite was determined by titration against triphenylphosphine : a known amount of PPh_3 was dissolved in DCM (roughly 0.1M) in a flamed-dried vial. Acetyl hypobromite solution was added dropwise until the solution turned from colorless to yellow or the PPh_3 was completely consumed as judged by TLC analysis. Concentrations typically ranged from 0.15 to 0.21M.

Note: Acetyl Hypobromite can also be prepared in DCM as described by Baran. However, for our purposes we found that DCM solutions had to be used immediately and several equivalents of acetyl hypobromite were necessary to fully brominate amide reagents.[26]

N-Bromination with Acetyl Hypobromite

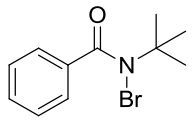


6

General Procedure : To a 250 mL flame dried, foil wrapped flask under N_2, amide (2.50 g, 8.0 mmol) was added followed by acetyl hypobromite solution (63 mL, 12.0 mmol, 0.21M) in CCl_4. The reaction was stirred at room temperature for 1-2 hours. When the reaction was complete as judged by ^{1}H NMR analysis (1.5 hours usually sufficient) the reaction was concentrated under reduced pressure to give a yellow solid. The crude material was recrystallized from cold acetone and water to give **6** (3.05g, 7.78 mmol, 98% yield) as pale yellow crystals.

General storage: All N-Bromo reagents were stored in foil-wrapped vials in the freezer when not in use. The reagents can be weighed out on the bench top without risk of decomposition.

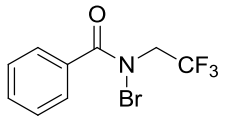
Analytical data for **Bromoamide 6**: **^{1}H NMR** (400MHz ,CHLOROFORM-d) δ = 8.09 (s, 2 H), 7.95 (s, 1 H), 1.60 (s, 9 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 173.72, 139.28, 131.93, 131.70, 131.48, 131.25, 128.55, 128.53, 125.68, 124.27, 124.25, 124.22, 124.20, 123.87, 122.06, 120.26, 64.41, 28.57 ppm; **IR** (thin film, cm^{-1}) 3337.2, 3090.4, 2982.4, 2938.0, 1670.1, 1538.9, 1383.6, 1281.5, 1182.2, 1138.1, 908.6, 847.6, 757.2, 702.9; **Elemental Analysis for** [$C_{13}H_{12}BrF_6NO$]; Theoretical = C: 39.82; H: 3.08; N: 3.57; Found = C: 40.09; H: 3.25; N: 3.69.



2

Bromoamide 2 was synthesized via the general procedure described above in 93% yield (800 mg) as dark yellow crystals.

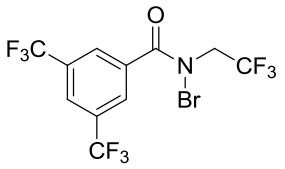
Analytical data for **Bromoamide 2**: **^{1}H NMR** (400MHz ,CHLOROFORM-d) δ = 7.69 - 7.62 (m, 2 H), 7.50 - 7.37 (m, 3 H), 1.60 - 1.55 (m, 9 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 177.17, 137.14, 130.90, 128.46, 127.89, 63.50, 28.70 ppm. **IR** (thin film, cm^{-1}) 2974.6, 2932.2, 1661.4, 1524.5, 1482.9, 1451.2, 1392.4, 1363.4, 1285.3, 1192.8, 1112.7, 1025.9, 795.5, 718.4, 695.2; **Elemental Analysis for** [$C_{11}H_{14}BrNO$]; Theoretical = C: 51.58; H: 5.51; N: 5.47; Found = C: 52.64; H: 5.75; N: 5.57.



3

Bromoamide 3 was synthesized via the general procedure described above in 94% yield (380 mg) as an off-white powder.

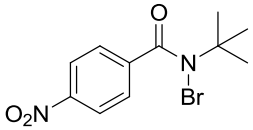
Analytical data for **Bromoamide 3**: **^{1}H NMR** (400MHz ,CHLOROFORM-d) δ = 7.59 - 7.50 (m, 3 H), 7.49 - 7.43 (m, 2 H), 4.40 (q, *J* = 8.1 Hz, 2 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 172.46, 132.23, 131.32, 128.52, 127.83, 126.40, 124.54, 122.68, 120.82, 55.62, 55.39, 55.16, 54.93 ppm; **IR** (thin film, cm^{-1}) 3321.8, 1664.3, 1630.5, 1352.8, 1255.4, 1142.6, 1066.4, 1022.1, 924.7, 787.8, 716.4, 700.0 621.9; **Elemental Analysis for** [$C_9H_7BrF_3NO$]; Theoretical = C, 38.32; H, 2.50; N, 4.97; Found = C: 38.50; H: 2.85; N: 4.84.



4

Bromoamide 4 was synthesized via the general procedure described above in 97% yield (1.2 g) as a colorless solid.

Analytical data for **Bromoamide 4**: **^{1}H NMR** (400MHz ,CHLOROFORM-d) δ = 8.06 (s, 2 H), 8.04 (s, 1 H), 4.48 (q, *J* = 8.1 Hz, 2 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 170.12, 134.75, 132.62, 132.28, 131.94, 131.62, 128.30, 125.01, 124.97, 124.83, 124.03, 122.05, 121.32, 55.00, 54.64, 54.29, 53.97 ppm; **IR** (thin film, cm^{-1}) 3289.9, 3095.2, 3008.4, 2965.0, 1823.4, 1659.5, 1397.2, 1377.9, 1342.2, 1279.5, 1259.2, 1151.3, 1056.8, 903.5, 847.5, 743.4, 702.9, 679.8, 563.1; **Elemental Analysis for** [$C_{11}H_5BrF_9NO$]; Theoretical = C: 31.60; H: 1.21; N: 3.35; Found = C: 31.59; H: 1.20; N: 3.42.

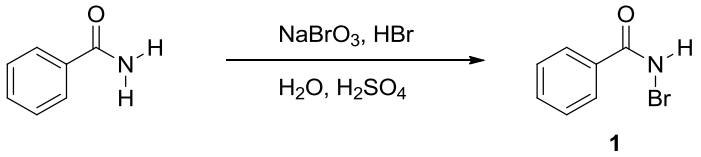


5

Bromoamide 5 was synthesized via the general procedure described above in 98% yield (1.7 g) as a bright yellow powder.

Analytical data for **Bromoamide 5: ^{1}H NMR** (400MHz ,CHLOROFORM-d) δ = 8.27 (d, *J* = 8.8 Hz, 1 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 1.60 (s, 9 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 174.47, 148.77, 143.26, 129.01, 123.22, 64.22, 28.61 ppm; **IR** (thin film, cm^{-1}) 3269.2, 3098.0, 2964.6, 1676.3, 1382.1, 1379.8, 1351.2, 1261.4, 1259.2, 1149.9, 1066.8, 903.2, 855.1, 740.7,

700.9, 689.1, 530.2; **Elemental Analysis for** [$C_{11}H_{13}BrN_2O_3$]; Theoretical = C: 43.87; H: 4.35; N: 9.30; Found = C: 44.01; H: 4.34; N: 9.11.

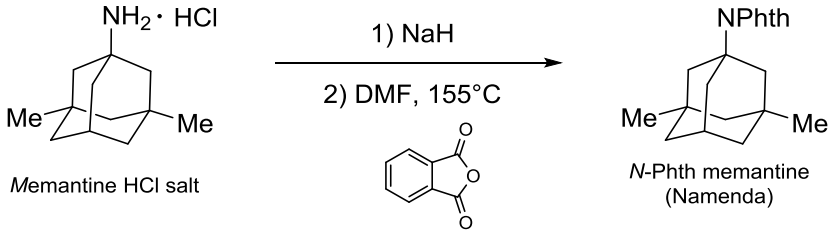


1

Bromoamide 1 was not synthesized using acetyl hypobromite, but instead via the procedure reported by Nishida and coworkers.[27] To a solution of benzamide (1.21g, 10mmol), sodium bromate (755 mg, 5mmol) and concentrated sulfuric acid (140uL, 2.5 mmol, 18.4M) in water, hydrobromic acid (750 uL, 47%, 6.7 mmol) was added with stirring. The reaction mixture was stirred an additional 10 min. The obtained precipitate was filtered with cold water and dried vacuum to give **1** (1.4 g, 6.8 mmol, 68% yield) as an off-white solid. Physical and spectral data were in accordance with literature data.

Substrate Synthesis

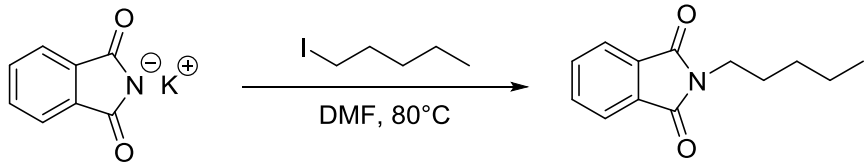
Note: Hydrocarbon substrates were obtained commercially and used without further purification unless otherwise noted.



***N*-Phth Memantine.** The hydrochloride salt (1.40 g, 5.6 mmol) was dissolved in DMF (15 mL) and cooled to 0 °C. Neat sodium hydride (134.4 mg, 5.6 mmol) was then added with gas evolution

and the reaction was stirred at 0 °C for 10 min. The reaction was then allowed to warm to room temperature over 30 min. Phthalic Anhydride (1.24 g, 8.37 mmol) was then added and the reaction was heated to reflux overnight. The reaction was then diluted with Et_2O and 1N HCl. The organic layer was separated and washed twice more with 1N HCl, and once with brine. The organic layer was then dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified using column chromatography (10% EtOAc/Hexanes) to isolate *N*-Phth Memantine (1.25 g, 3.92 mmol, 70% yield) as a white solid.

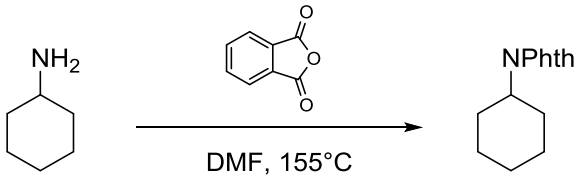
Analytical data for ***N*-Phth Memantine:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.80 - 7.72 (m, 2 H), 7.71 - 7.63 (m, 2 H), 2.36 (br. s., 2 H), 2.28 - 2.21 (m, 1 H), 2.16 (s, 4 H), 1.49 (d, *J* = 12.5 Hz, 2 H), 1.34 (d, *J* = 12.1 Hz, 2 H), 1.31 - 1.24 (m, 1 H), 1.24 - 1.15 (m, 1 H), 0.91 (s, 6 H); **^{13}C NMR** (125 MHz ,CHLOROFORM-d) δ = 169.8, 133.6, 131.9, 122.5, 61.8, 50.3, 46.0, 42.5, 38.7, 32.6, 32.6, 30.4, 30.3 ppm, **IR** (thin film, cm^{-1}) 3460.6, 2944.1, 2866.2, 1769.4, 1708.6, 1613.2, 1454.1, 1361.5, 1351.2, 1156.1, 1081.9, 1051.9, 871.7, 788.7, 717.4, 644.1; **HRMS** (ESI) Calcd. for $[C_{20}H_{23}NO_2+H]^+$ = 310.17, Found = 310.21.



***N*-Pentyl Phthalimide** was synthesized via an alkylation reaction of iodopentane with phthalimide potassium salt: To a room temperature solution of iodopentane (2.5 mL, 19.14 mmol) in DMF (200 mL), the phthalimide salt (7.09 g, 38.3 mmol) was added. The reaction was headed to 80 °C overnight. The reaction was cooled to room temperature and diluted with Et_2O and water. The

organic layer was separated and washed 8 times with 100 mL of water to remove the residual phthalimide salt. The organic layer was then dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified using column chromatography (25% EtOAc/Hexanes) to isolate N-Phth pentane (3.45 g, 15.5 mmol, 82% yield) as a clear, yellowish liquid.

Analytical data for ***N*-Pentyl Phthalimide:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.88 - 7.75 (m, 1 H), 7.73 - 7.59 (m, 2 H), 3.74 - 3.56 (m, 2 H), 1.75 - 1.57 (m, 2 H), 1.31 (br. s., 4 H), 0.94 - 0.79 (m, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.4, 133.8, 132.1, 123.1, 37.9, 28.9, 28.2, 13.9 ppm; **IR** (thin film, cm^{-1}) 3468.4, 3061.4, 2934.2, 1773.2, 1712.5, 1614.13, 1465.6, 1397.2, 1367.3, 1186.0, 1058.7, 980.6880.3, 793.5, 719.3, 620.0, 530.3; **HRMS** (ESI) Calcd. for $[C_{13}H_{15}NO_2+H]^+$ = 218.11, Found = 218.04.

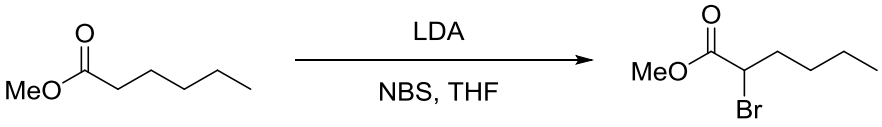


***N*-Phth Cyclohexane** was synthesized via a condensation reaction between cyclohexylamine and phthalic anhydride: To a solution of cyclohexylamine (1.0 g, 10.08 mmol) in DMF (15 mL), phthalic anhydride (2.24 g, 15.12 mmol) was added and the reaction was heated to reflux overnight. The reaction was cooled slowly to room temperature and the product crystalized out of solution. To the reaction mixture, 20 mL of 1N HCl was added and the reaction was put in the freezer for 20 min. The product was then filtered off using vacuum filtration and washed twice more with 1N HCl. The product was then dried under reduced pressure for several hours. This

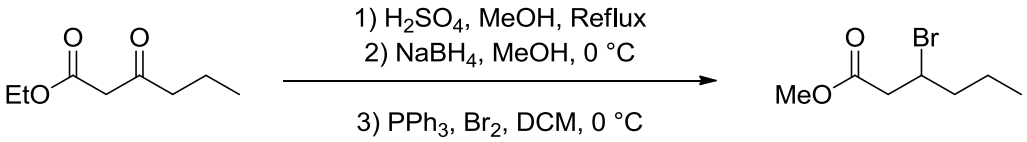
yielded analytically pure *N*-Phth Cyclohexane (2.02 g, 8.8 mmol, 87% yield) as a white crystalline solid. Physical and spectral data were in accordance with literature data.[28]

Synthesis of Bromide Standards

Note: Bromide standards were obtained commercially and used without further purification unless otherwise noted. Commercially obtained bromides include: bromocyclohexane, bromocyclopentane, bromocycloheptane, 2-exo-bromonorbornane, 1-bromoadamantane, 2-bromoadamantane.

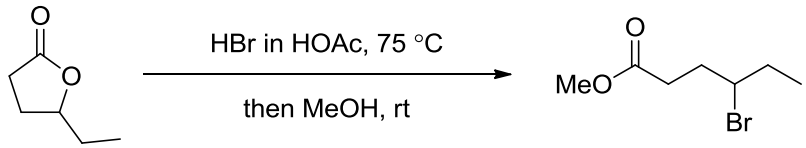


Methyl 2-bromohexanoate : A solution of nBuLi in hexanes (3.27 mL, 2.6M, 23.0 mmol) was added dropwise to a -78 °C solution of diisopropylamine (3.27 mL, 23.0 mmol) in THF (30 mL). The solution was warmed to 0 °C, stirred for 15 min and, cooled to -78 °C again and methyl hexanoate (2.50 g, 19.2 mmol) was added. The reaction was allowed to warm to 0 °C and was stirred for 20 min. The enolate solution was then transferred via cannula into a suspension of *N*-bromosuccinimide (4.1 g, 23.0 mmol) in THF (42 mL) at -78 °C. The reaction mixture was allowed to warm to room temperature slowly overnight, then was concentrated under reduced pressure. The crude material was purified using column chromatography (2-5% EtOAc/Hexanes gradient) to isolate methyl 2-bromohexanoate (2.05g, 9.8 mmol, 51% yield) as a yellow oil. Physical and spectral data were in accordance with commercially available material.

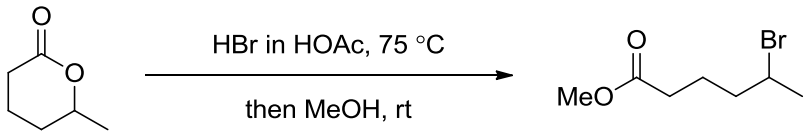


Methyl 3-bromohexanoate: A solution of ethyl 3-oxohexanoate (2.5 g, 15.7 mmol) and concentrated sulfuric acid (110 μL) in methanol (35 mL) was heated to reflux for 8 hours until complete consumption of the starting material was determined by TLC analysis. The reaction mixture was then partially concentrated under reduced pressure, taken up in Et_2O, and washed with brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure to give methyl 3-oxohexanoate (1.45 g, 64% yield) as a yellow orange liquid that was used in the next step without purification. Sodium borohydride (541 mg, 14.3 mmol) was added to a -78 °C solution of crude methyl 3-oxohexanoate (1.03 g, 7.14 mmol) in methanol (60 mL). The reaction was stirred cold for 1.5 hours then warmed to room temperature, extracted three times with DCM and two times with Et_2O. The combined organic layers were washed with brine, dried with magnesium sulfate and concentrated under reduced pressure to give methyl 3-hydroxyhexanoate (903 mg, 87% yield). Crude methyl 3-hydroxyhexanoate (903 mg, 6.18 mmol) was added to a 0 °C solution of bromine (348 μL, 6.80 mmol) and triphenylphosphine (1.81 g, 6.80 mmol) in DCM (30 mL). The reaction was allowed to stir for 4 hours at 0 °C until complete consumption of starting material was determined by TLC analysis. The reaction mixture was then quenched with water, the aqueous layer extracted with DCM and the combined organic layers washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The crude bromide product was purified using column chromatography (5% EtOAc/Hexanes) to isolate methyl 3-bromohexanoate (660 mg, 51% yield) as a clear, colorless liquid.

Analytical data for **β-Bromohexanoate:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 4.40 - 4.28 (m, 1 H), 3.76 - 3.66 (m, 3 H), 2.89 (d, *J* = 7.3 Hz, 2 H), 1.89 - 1.72 (m, 2 H), 1.63 - 1.51 (m, 1 H), 1.51 - 1.40 (m, 1 H), 0.93 (t, *J* = 7.5 Hz, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 170.8, 51.9, 49.7, 44.1, 40.7, 20.7, 13.3 ppm; **IR** (thin film, cm^{-1}) 1743.3, 1436.7, 1375.9, 1355.7, 1310.4, 1253.5, 1012.5, 934.3, 749.2; **HRMS** (ESI) Calcd. for $[C_7H_{13}BrO_2+H]^+$ = 209.01, Found = 208.97

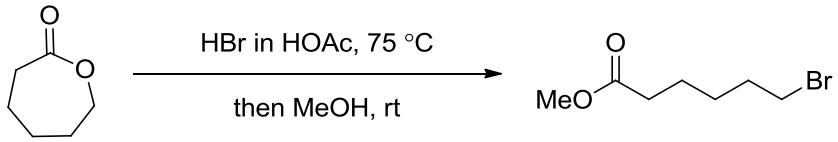


Methyl 4-bromohexanoate: This procedure is adapted from the method reported by Wolf et. al.[29] Gamma-caprolactone (2.0 g, 17.5 mmol) was added to a flask containing a solution of 33% HBr in AcOH (5 mL) and fitted with a reflux condenser. The reaction was heated to 75 °C for 4 hours then cooled to room temperature, at which point methanol (8.0 mL) was added and the mixture was stirred at room temperature overnight. The reaction was then partially concentrated under reduced pressure, taken up in EtOAc, washed three times with a saturated aqueous solution of sodium bicarbonate, brine, and the organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified using column chromatography (5% EtOAc/Hexane) to isolate methyl 4-bromohexanoate (2.20 g, 61% yield) as a clear liquid. Physical and spectral data were in accordance with literature data.[30]

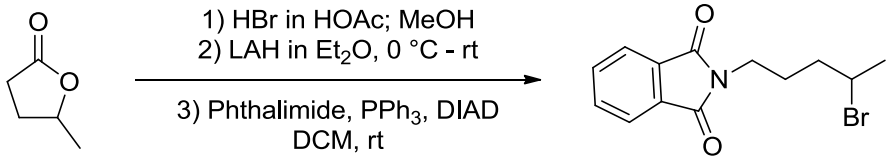


Methyl 5-bromohexanoate: was synthesized via lactone opening with HBr using a method identical to the one described for methyl 4-bromohexanoate above in 72% yield (2.05 g).

Analytical data for **δ-Bromohexanoate:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 4.11 (sxt, *J* = 6.5 Hz, 1 H), 3.66 (s, 3 H), 2.33 (t, *J* = 7.2 Hz, 2 H), 1.92 - 1.78 (m, 3 H), 1.77 - 1.72 (m, 1 H), 1.70 (d, *J* = 7.3 Hz, 3 H); **^{13}C NMR** (125 MHz ,CHLOROFORM-d) δ = 173.6, 51.6, 50.8, 40.2, 33.2, 26.4, 23.1 ppm; **IR** (thin film, cm^{-1}) 1739.5, 1438.6, 1376.9, 1199.5, 10096.6, 982.5, 860.1, 773.3; **HRMS** (ESI) Calcd. for $[C_7H_{13}BrO_2+H]^+$ = 209.01, Found = 209.02



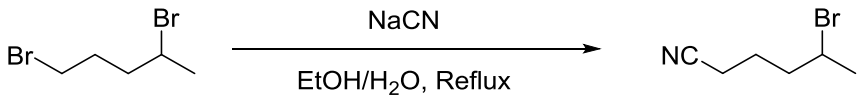
Methyl 6-bromohexanoate was synthesized via lactone opening with HBr using a method identical to the one described for methyl 4-bromohexanoate above in 95% yield (1.73 g). Physical and spectral data were in accordance with literature data.[9]



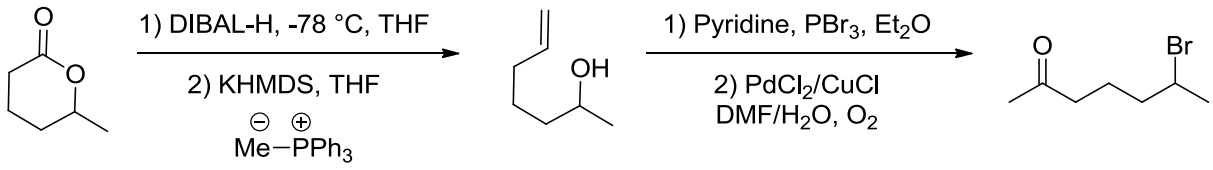
***N*-4-bromopentyl phthalimide** was synthesized via the following three step protocol. The initial step involves lactone opening with HBr using a method identical to the one described above in 83% yield (1.85 g). A solution of lithium aluminum hydride (4.0 mL, 4.0 mmol, 1.0M in Et_2O) was added dropwise to a 0 °C solution of methyl 4-bromopentanoate (500 mg, 2.57 mmol) in Et_2O

(10 mL). The reaction was allowed to reach room temperature and stirred for 7 hours until TLC showed complete consumption of the starting material. The reaction was quenched by the sequential slow addition of water (150 μL), 2.5M NaOH solution (300 μL), and water (450 μL). The insoluble salts were removed via suction filtration and the reaction was concentrated under reduced pressure to 4-bromopentanol (350 mg, 82% yield) which was used in the next step without further purificationTriphenylphosphine (826 mg, 3.15 mmol) and phthalimide (463 mg, 3.15 mmol) were added to a solution of 4-bromopentanol (350 mg, 2.1 mmol) in THF (20 mL). Diisopropylazodicarboxylate (620 μL, 3.15 mmol) was then added dropwise and the reaction was allowed to stir at room temperature overnight. The reaction was then concentrated under reduced pressure and the crude reaction mixture was purified using column chromatography (10-20% EtOAc/Hexanes gradient) to give *N*-4-bromopentyl phthalimide (601 mg, 2.0 mmol, 96% yield) as a clear yellow oil.

Analytical data for **(δ)-Bromopentylphthalimide: ^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.92 - 7.80 (m, 2 H), 7.78 - 7.65 (m, 2 H), 4.25 - 4.09 (m, 1 H), 3.73 (t, *J* = 6.4 Hz, 2 H), 2.00 - 1.78 (m, 4 H), 1.71 (d, *J* = 6.6 Hz, 3 H); **^{13}C NMR** (125 MHz ,CHLOROFORM-d) δ = 168.4, 133.9, 132.1, 123.3, 50.6, 38.1, 37.2, 27.0, 26.5 ppm; **IR** (thin film, cm^{-1}) 3465.5, 3061.4, 1773.2, 1711.6, 1614.1, 1438.6, 1398.1, 1365.4, 1244.8, 1188.9, 1147.4, 1077.2, 1032.6, 901.5, 720.3, 619.4, 530.3; **HRMS** (ESI) Calcd. for $[C_{13}H_{14}BrNO_2+H]^+$ = 296.02, Found = 296.03**.**



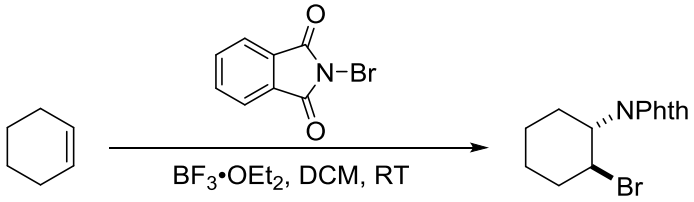
2-Bromo-5-Cyanopentane was prepared via the method reported by Oae.[31] Sodium cyanide (1.79 g, 36.5 mmol) was added to a boiling solution of EtOH (10 mL) and 1,4-dibromopentane (4.10 mL, 30.0 mmol). The reaction was stirred vigorously at reflux for 3 hours then cooled to room temperature. The ethanol was then directly distilled off and the remaining reaction mixture was poured into water. The oil was separated from the aqueous layer and dried with calcium chloride. The crude reaction mixture was distilled from calcium chloride (75-80 °C, 6 torr) to give 2-bromo-5-cyanopentane (3.26 g, 57% yield) as a pale liquid.



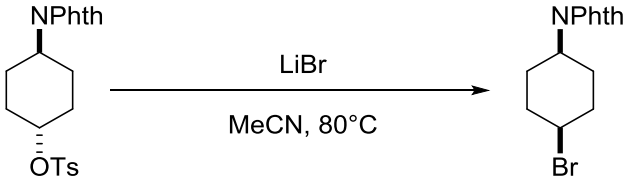
6-Bromoheptan-2-one was synthesized via the four step procedure shown above. The synthesis of hept-6-en-2-ol was performed as outlined by Perez-Castells et. al..[32] To a 0 °C solution of PBr_3 (150 μL, 1.57 mmol) in Et_2O (4 mL) was added a solution of hept-6-en-2-ol (450 mg, 3.94 mmol) and pyridine (158 μL, 1.57 mmol) in Et_2O (1 mL) dropwise. The reaction mixture was stirred at 0 °C for 5 hours then quenched with ice water, extracted with Et_2O, dried with magnesium sulfate and concentrated under reduced pressure. (*Note: If dibromophosphoric acid remains the reaction can be worked up with aqueous HBr to more fully convert the dibromophosphoric acid and improve the yield of the desired product.)* The product was purified using column chromatography (5% EtOAc/Hexanes) to give 6-bromohept-1-ene (120 mg, 23% yield) as a yellow oil. In a 10 mL round bottom flask palladium dichloride (8.0 mg, 0.045 mmol) and copper (I) chloride (46.0 mg, 0.43 mmol) were dissolved in DMF/H_2O (600 μL, 7:1) solution and stirred under O_2 (1 atm) for 1 hour.. A DMF/H_2O (200 μL, 7:1) solution of 6-bromohept-1-ene (120 mg, 0.678 mmol) was then added and the reaction mixture was allowed to stir overnight at room temperature. The reaction

was quenched with 30% potassium bicarbonate solution (color change to green), diluted with Et_2O, washed again with sodium bicarbonate, dried with magnesium sulfate and concentrated under reduced pressure. 6-bromoheptan-2-one (25 mg, 21% yield) was characterized without purification. Analytical data was consistent with literature data.[33]

Analytical data for **6-bromoheptan-2-one: ^{1}H NMR** (400MHz ,CHLOROFORM-d) δ = 4.09 (sxt, *J* = 6.5 Hz, 1 H), 2.97 - 2.82 (m, 1 H), 2.48 - 2.41 (m, 2 H), 2.12 (s, 3 H), 1.83 - 1.71 (m, 3 H), 1.69 (d, *J* = 6.5 Hz, 3 H); **HRMS** (ESI) Calcd. for $[C_7H_{13}BrO+H]^+$ = 193.01, Found = 193.20



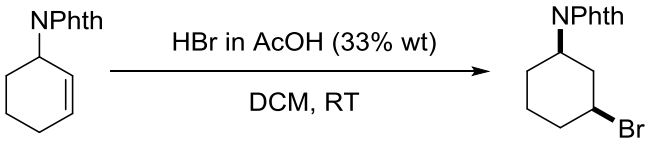
1,2-*trans* bromocyclohexyl phthalimide was synthesized via the bromoimidiation of cyclohexene. N-Bromophthalimide (44.98 mg, 0.2 mmol) was dissolved in 1 mL of DCM and cyclohexene was added (30.38 uL, 0.3 mmol). The BF_3•OEt_2 (24 uL, 0.2 mmol) was then added and the reaction was stirred at room temperature in the dark for 20 minutes. The reaction was concentrated under reduced pressure and purified directly using column chromatography (10% EtOAc/Hexanes) to give the product as a colorless solid (40.0 mg, 0.13 mmol 65% yield). Analytical data were consistent with literature data.[34]



1,4-*cis* bromocyclohexyl phthalimide was synthesized via an S_N2 reaction on the corresponding tosylate (the tosylate was prepared via dual protection of the commercially available amino

alcohol). To a solution of tosylate (100 mg, 0.25 mmol) in dry acetonitrile (5mL), dry lithium bromide was added (21.8 mg, 0.25 mmol) and the solution was heated to reflux overnight. The reaction showed only partial conversion to a mixture of the undesired elimination product as well as the desired bromide. After removal of the remaining lithium bromide with a water/Et_2O extraction, the reaction was concentrated under reduced pressure and purified using column chromatography (10-15% EtOAc/Hexanes) to obtain the bromide standard (24.6 mg, 0.08 mmol, 32% yield) as a white powder.

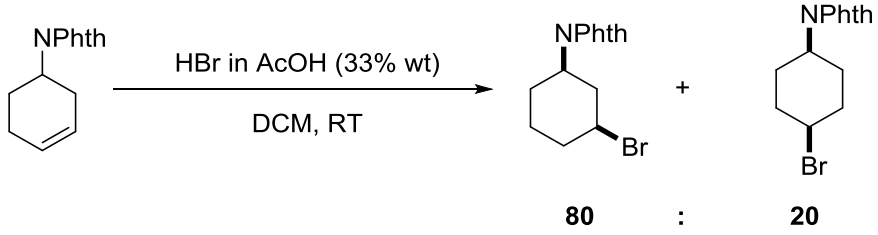
Analytical data for **1,4-*cis* bromocyclohexyl phthalimide:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.95 - 7.82 (m, 2 H), 7.79 - 7.66 (m, 2 H), 4.68 (d, *J* = 2.6 Hz, 1 H), 4.28 - 4.09 (m, 1 H), 2.87 (dq, *J* = 3.3, 12.8 Hz, 2 H), 2.32 - 2.19 (m, 2 H), 2.03 - 1.88 (m, 2 H), 1.68 - 1.61 (m, 2 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.2, 133.9, 131.9, 123.1, 51.4, 49.7, 34.6, 24.4 ppm; **IR** (thin film, cm^{-1}) 3459.7, 2254.4, 1767.4, 1701.6, 1465.6, 1375.0, 1253.5, 1114.65, 1059.7, 1020.2, 908.3, 719.3, 531.2; **HRMS** (ESI) Calcd. for $[C_{14}H_{14}BrNO_2+H]^+$ = 308.02, Found = 307.97.



1,3-*cis* bromocyclohexyl phthalimide was synthesized via the stereoselective HBr addition to the unsaturated cyclohexyl phthalimide shown above (prepared from corresponding alkenol). To a solution of alkene (100 mg, 0.44 mmol) in 100 uL of DCM the HBr solution (500 uL, 33% wt) was added dropwise. The reaction was allowed to stir at room temperature for 4 hours and was quenched with pentane and water (exothermic). The organic layer was washed three times with a saturated sodium bicarbonate solution, brine, dried with magnesium sulfate and concentrated under

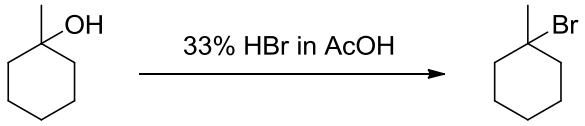
reduced pressure. The product was a colorless solid and was obtained in a single isomer and no purification was required (128 mg, 0.41 mmol, 95% yield). *The spectral data was consistent with the same product prepared via substitution of the tosylate in the manner described above.*

Analytical data for **1,4-*cis* bromocyclohexyl phthalimide:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.89 - 7.77 (m, 14 H), 7.76 - 7.64 (m, 2 H), 4.89 - 4.69 (m, 2 H), 2.90 - 2.79 (m, 1 H), 2.21 (dq, *J* = 3.9, 12.7 Hz, 1 H), 2.15 - 1.97 (m, 3 H), 1.90 - 1.70 (m, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.3, 133.9, 131.9, 123.2, 53.3, 46.0, 37.3, 33.4, 29.4, 20.7 ppm; **IR** (thin film, cm^{-1}) 3465.5, 2867.6, 1772.3, 1712.5, 1614.13, 1438.6, 1397.1, 1366.0, 1244.8, 1188.9, 1073.2, 1032.7, 882.3, 720.3, 619.0; **HRMS** (ESI) Calcd. for $[C_{14}H_{14}BrNO_2+H]^+$ = 308.02, Found = 308.06

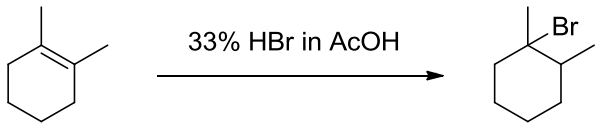


1,3 and 1,4 -*cis* bromocyclohexyl phthalimides were synthesized as a mixture via HBr addition to the alkene shown above (alkene prepared via the route described by Anderson et. al.[35]). To a solution of alkene (100 mg, 0.44 mmol) in 100 uL of DCM the HBr solution (500 uL, 33% wt) was added dropwise. The reaction was allowed to stir at room temperature for 4 hours and was quenched with pentane and water (exothermic). The organic layer was washed 3 x with a saturated sodium bicarbonate solution, 1x with brine, dried with magnesium sulfate and concentrated under reduced pressure. The product was a colorless solid and was obtained as an 80:20 mixture of two isomers (121 mg, 92% yield). Further purification was not required.

Analytical data for **1,3 and 1,4 -*cis* bromocyclohexyl phthalimides: ^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.88 - 7.77 (m, 2 H), 7.75 - 7.63 (m, 2 H), 4.87 - 4.70 (m, 1.6 H), 4.66 (t, *J* = 2.9 Hz, 0.2 H), 4.22 - 4.09 (m, 0.2 H), 2.91 - 2.77 (m, 1.2 H), 2.30 - 1.70 (m, 6.8 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.3, 134.0, 133.9, 133.8, 123.1, 53.3, 51.5, 49.7, 46.0, 37.4, 37.3, 34.3, 33.4, 29.4, 24.4, 20.7 ppm; **IR** (thin film, cm^{-1}) 3465.2, 2871.8, 1770.0, 1715.2, 1594.8, 1441.4, 1399.1, 1364.0, 1239.3, 1189.4, 1075.4, 1029.4, 886.5, 720.2; **HRMS** (ESI) Calcd. for $[C_{14}H_{14}BrNO_2+H]^+$ = 308.02, Found = 308.02

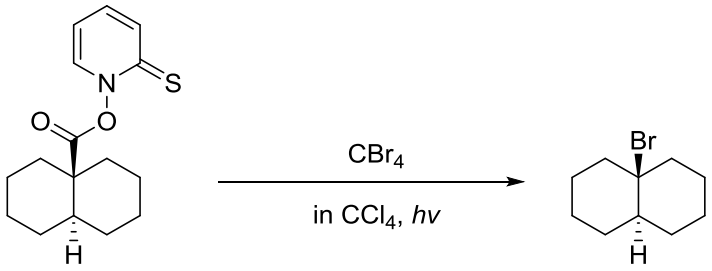


1-Bromo-1-Methylcyclohexane was synthesized according to literature procedures[36] and used without purification. Physical and spectral data were in accordance with literature data.[37]



1-Bromo-1,2-Dimethylcyclohexane was synthesized via HBr addition to the corresponding alkene. A solution of HBr in AcOH was added (550 μL, 33% wt) dropwise to 1,2-dimethylcyclohex-1-ene (100 μL, 0.908 mmol) in a 10 mL round bottom flask under N_2. The reaction was allowed to stir at room temperature for 2 hours. The reaction was then diluted with pentane, and water (note: this causes an exothermic reaction). The organic layer was separated and washed three times with a saturated sodium bicarbonate solution, water, dried with magnesium sulfate and concentrated under reduced pressure. Both NMR and GC analysis show both the *trans* and *cis* products in a 87:13 ratio respectively. The selectivity is consistent with literature precedent.[38]

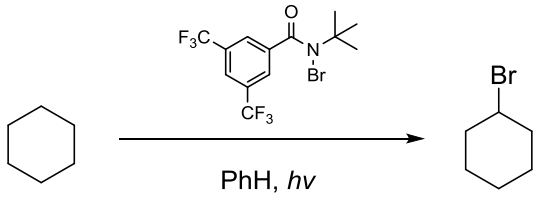
Analytical data for **1-Bromo-1,2-Dimethylcyclohexane: ^{1}H NMR** (400MHz ,CHLOROFORM-d) δ = 2.19 - 2.10 (m, 3 H), 1.80 - 1.73 (m, 10 H), 1.66 - 1.51 (m, 5 H), 1.51 - 1.34 (m, 8 H), 1.34 - 1.21 (m, 6 H), 1.10 (d, *J* = 7.0 Hz, 1 H *normalized to this signal for cis trans ratio*), 1.03 - 0.98 (m, 3 H); **^{13}C NMR** (100MHz ,CHLOROFORM-d) δ = 78.2, 26.1, 44.9, 43.9, 43.8, 34.1, 33.3, 31.9, 31.7, 31.6, 25.7, 24.6, 23.5, 19.2, 18.5, 18.1, 14.0 ppm; **IR** (thin film, cm^{-1}) 2933.2, 2857.0, 1447.3, 1376.9, 1259.5, 1137.8, 1077.1, 1005.7, 816.7.



(4as,8as)-4a-bromodecahydronaphthalene was synthesized via the exact procedure reported by Dauben et. al.[39] Physical and spectral data were in accordance with literature data. The *cis* isomer was obtained as a mixture with the *trans* compound via HBr addition to the tetrasubstituted alkene.[40,41]

2.5.3 C-H Bromination Procedures with N-Bromoamides

Bromination of Cycloalkanes

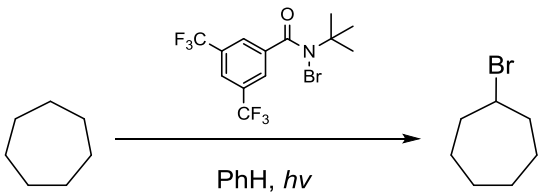


A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and

the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (200 μL). Cyclohexane (5.5 μL, 0.051 mmol) was then added. *Note: cycloalkane was added as a stock solution in benzene to improve the reproducibility of the results.* The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 30 minutes. A white, semi-soluble precipitate forms as the reaction reaches completion. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 70.8% GC yield of cyclohexylbromide.

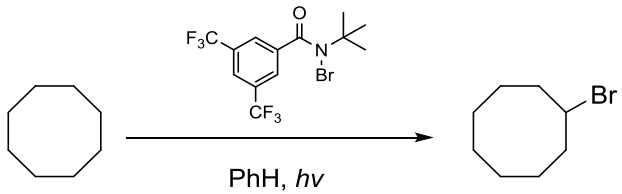
The reaction was repeated on 0.5 mmol scale using 200 mg of bromoamide in 2 mL of dry, freeze-pump-thawed benzene. Cyclohexane (52.5 uL, 0.51 mmol) was then added and the reaction was performed as described above (but was let run overnight), giving 68.8% GC yield of Cyclohexylbromide.

Reactions with other bromoamides in **Table 2-1.** Bromination of cyclohexane with various *N-bromoamidesawere performed in an identical fashion to the procedure described above.*

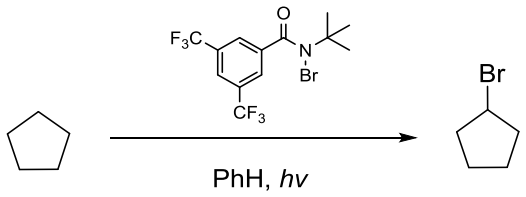


A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (200 μL). Cycloheptane (6.2 μL, 0.051 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room

temperature) and irradiated with two 100W tungsten filament lightbulbs for 30 minutes. Upon competition, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 75.3% GC yield of cycloheptylbromide.



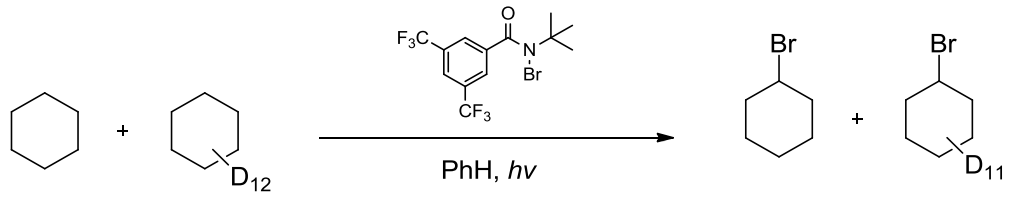
A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (200 μL). Cyclooctane (6.8 μL, 0.051 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 30 minutes. Upon competition, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 75.3% GC yield of cyclooctylbromide



A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (200 μL). Cyclopentane (4.8 μL, 0.051 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room

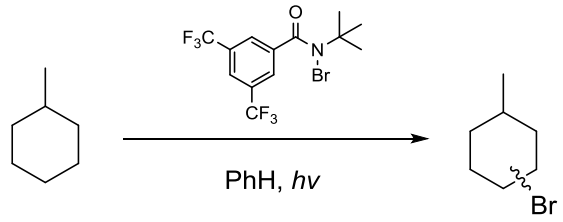
temperature) and irradiated with two 100W tungsten filament lightbulbs for 30 minutes. Upon competition, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 54.1% GC yield of cyclopentylbromide.

KIE Study



A flame-dried, 1 dram vial was charged with a stir bar and fitted with a PTFE lined screw cap. Bromoamide (20 mg, 0.051 mmol) was added to the vial in the absence of ambient light, and the reaction was taken into a glovebox, and dissolved in 200 uL of dry, freeze-pump-thawed benzene. Cyclohexane (27.6 uL, 0.255 mmol) and Cyclohexane-d_{12} (27.5 uL, 0.255 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 1 hour. The reaction was then diluted with DCM and analyzed using an Agilent Gas Chromatograph- Mass Spectrometer with a 6850 series GC system and a 5973 Network Mass Selective Detector to determine the ratio of non-deuterated to deuterated product (Ratio = 5.8 = $K_{H/D}$).

Bromination of Methylcyclohexane



Methylcyclohexane: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (200 μL). Methylcyclohexane (6.5 μL, 0.051 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The approximate yield was also verified with NMR analysis using 2,5 dimethylfuran as an internal standard. 75% GC yield of combined bromide products.

Figure 2-6. Bromination of Methylcyclohexane gas chromatogram

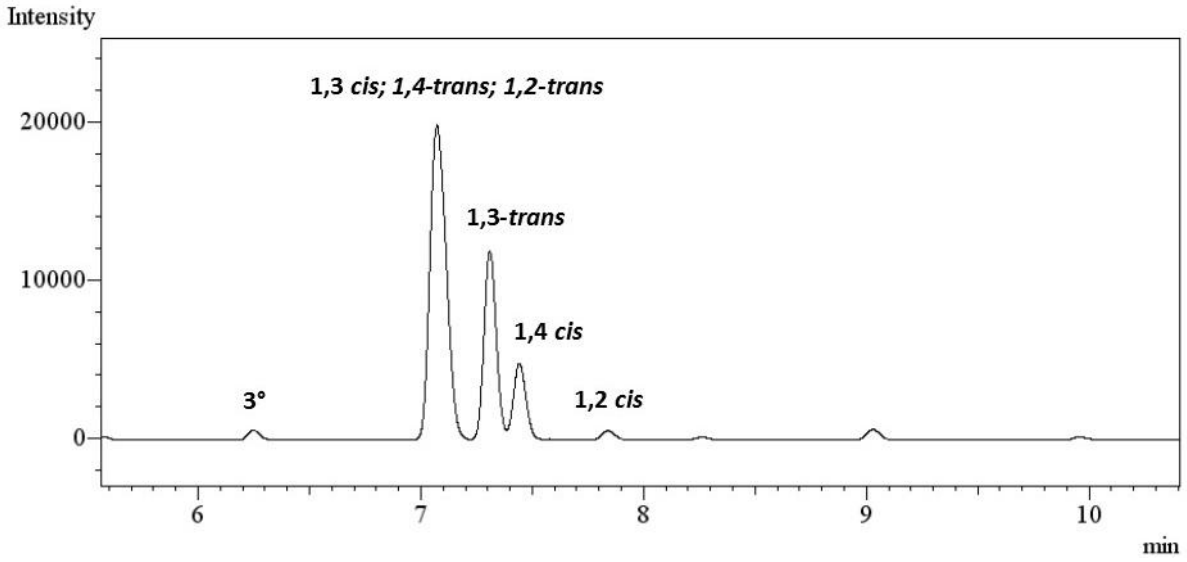


Figure 2-7. Overlaid gas chromatogram of bromination of methylcyclohxane with authentic 3° product

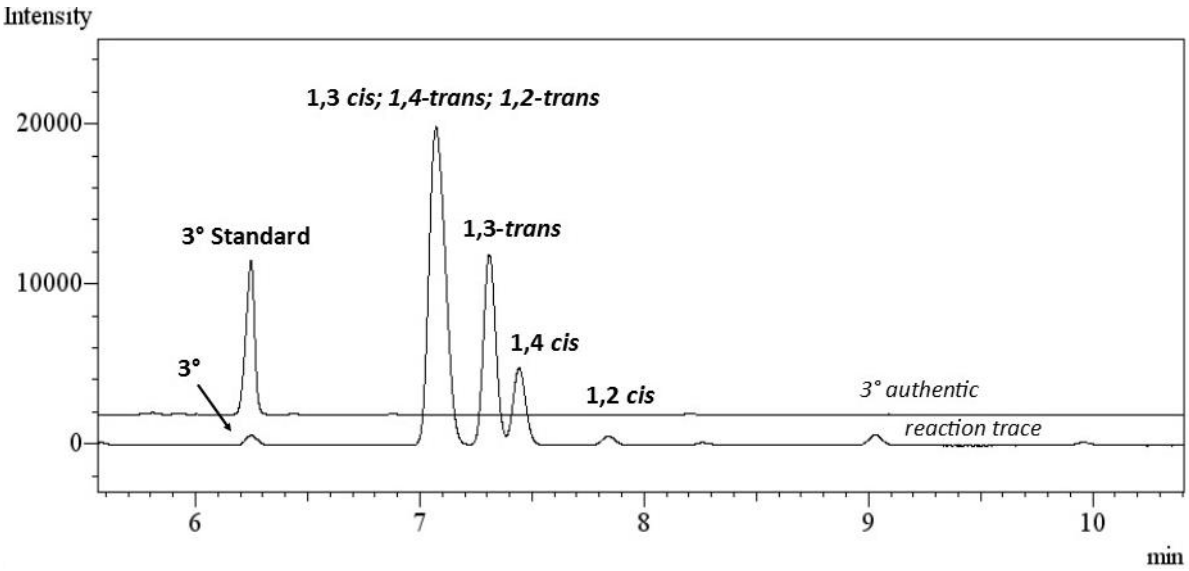
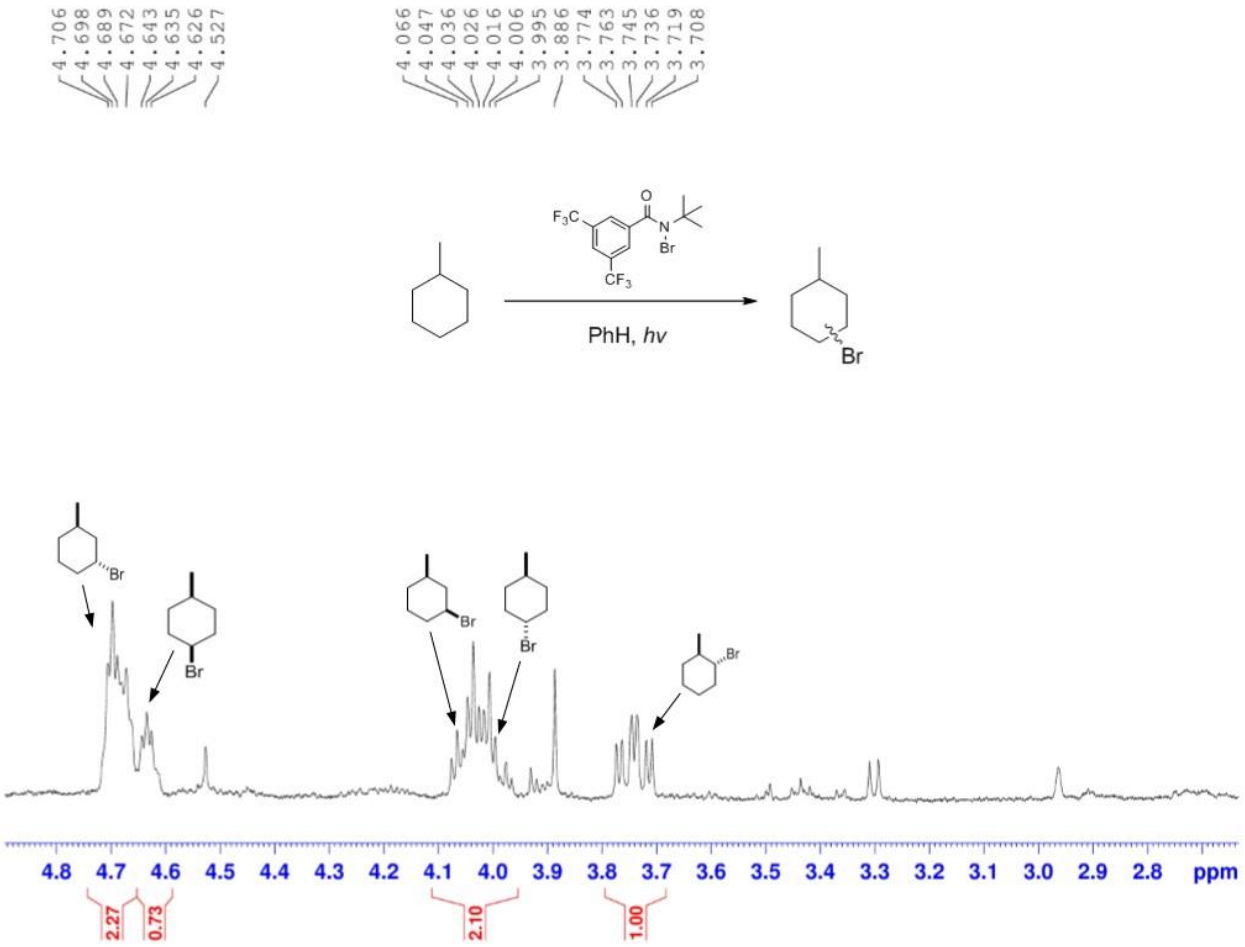


Table 2-8. Selectivity for bromination of methyl cyclohexane with bromoimide 6

Chromatogram Data		
Product	Retention Time	Percent Area
3° bromide	6.25	1.36
1,3-*cis;* 1,4-*trans;* 1,2-*trans*	7.07	60.19
1,3-*trans*	7.31	27.38
1,4-*cis*	7.44	11.05
1,2-*cis*	7.82	Trace

Figure 2-8. Crude NMR of reaction of methylcyclohexane with bromoamide 6



The NMR spectrum of the crude reaction mixture allowed for the determination of the distribution of secondary bromides formed in the bromination of methylcyclohexane with N-bromo reagent 6.

The relative chemical shifts and splitting patterns are nearly identical to those previously reported for methylcyclohexanols.[42]

HBr addition to the related alkenes (in conjunction to NMR analysis) were used to help identify which isomers corresponded to each peak in the GC trace. The product distributions change based on the regioisomer of the alkene starting material.

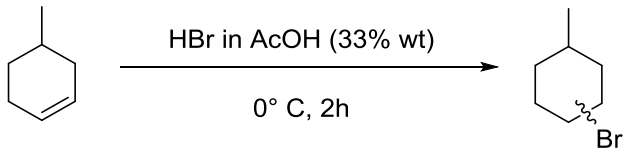


Table 2-9. Bromination of 1-methyl-3-cyclohexane

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
3° bromide	6.25	0.70
1,3-*cis;* 1,4-*trans;* 1,2-*trans*	7.07	2.67
1,3-*trans*	7.31	44.61
1,4-*trans*	7.44	48.32
1,2-*cis*	7.82	3.68

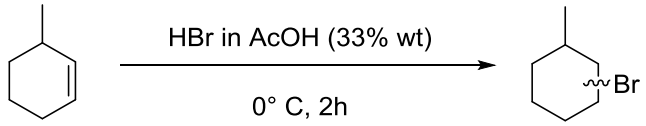
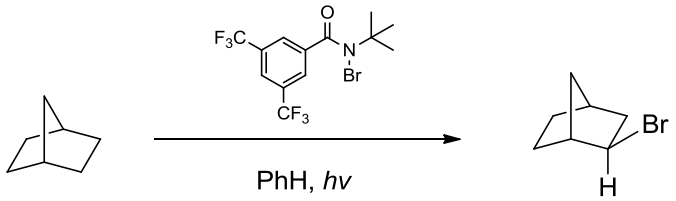


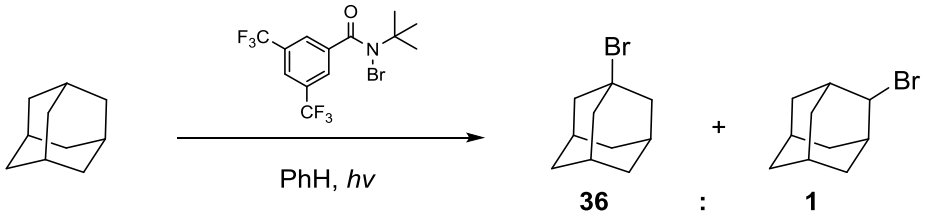
Table 2-10. Bromination of 1-methyl-2-cyclohexane

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
3° bromide	6.25	----
1,3-*cis;* 1,4-*trans;* 1,2-*trans*	7.07	9.61
1,3-*trans*	7.31	49.27
1,4-*trans*	7.44	5.48
1,2-*cis*	7.82	35.63

Bromination of Complex, Cyclic Alkanes

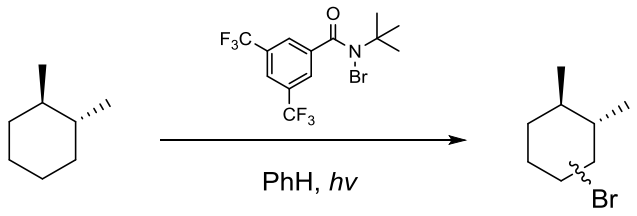


Norbornane: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (200 μL). Norbornane (4.9 mg, 0.051 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The reaction gives only the 2-exo product. 63.1% GC yield of 2-*exo*-Bromonorbornane.



Adamantane: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (200 μL). Adamantane (6.9 mg, 0.051 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath

(roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The reaction gives both 1-and 2-Bromoadamante in a 36 to 1 ratio by GC respectively. 58.4% GC yield of combined Bromoadamantanes.



1,2-*trans*-dimethylcyclohexane: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (45.0 mg, 0.114 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (300 μL). 1,2-*trans*-dimethylcyclohexane (11.1 μL, 0.076 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was run through a plug of silica and concentrated a second time. The reaction was analyzed by NMR using 2,5-dimethylfuran as an internal standard to determine the yield of secondary bromide products. GC analysis was used to determine the relative amount and yield, of the tertiary bromide products. 53.0% NMR yield of combined bromide products.

Figure 2-9. Bromination of *trans*-1,2-dimethylcyclohexane gas chromatogram

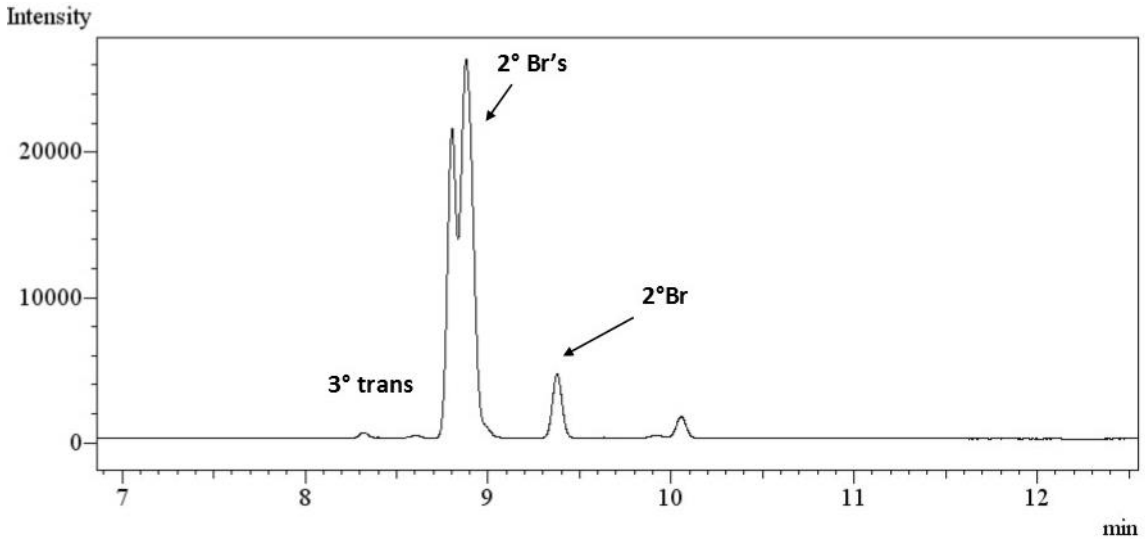


Figure 2-10. Overlaid gas chromatogram for bromination of *trans*-1,2-dimethylcyclohexane with authentic 3^{o} products

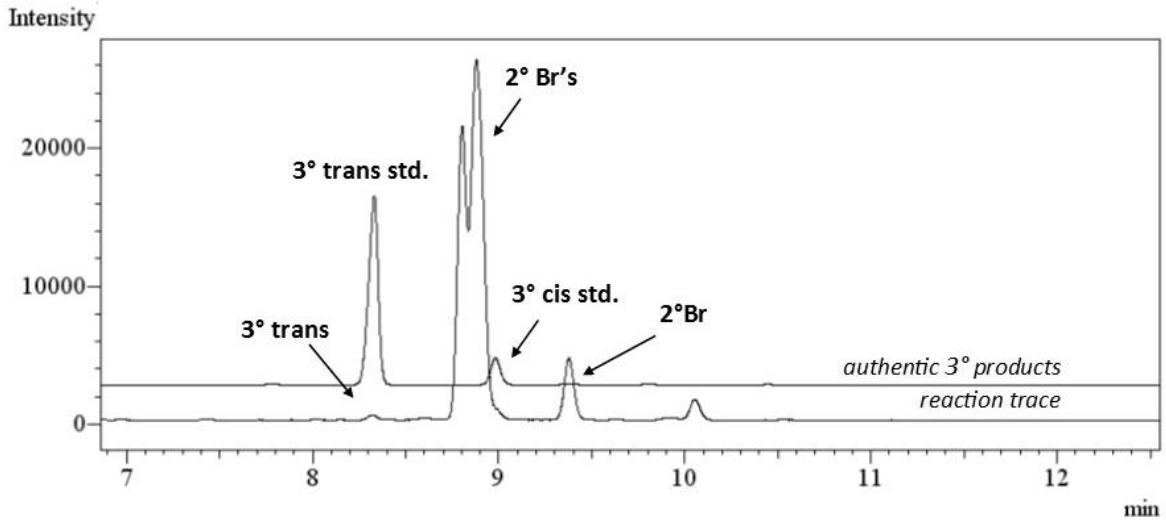
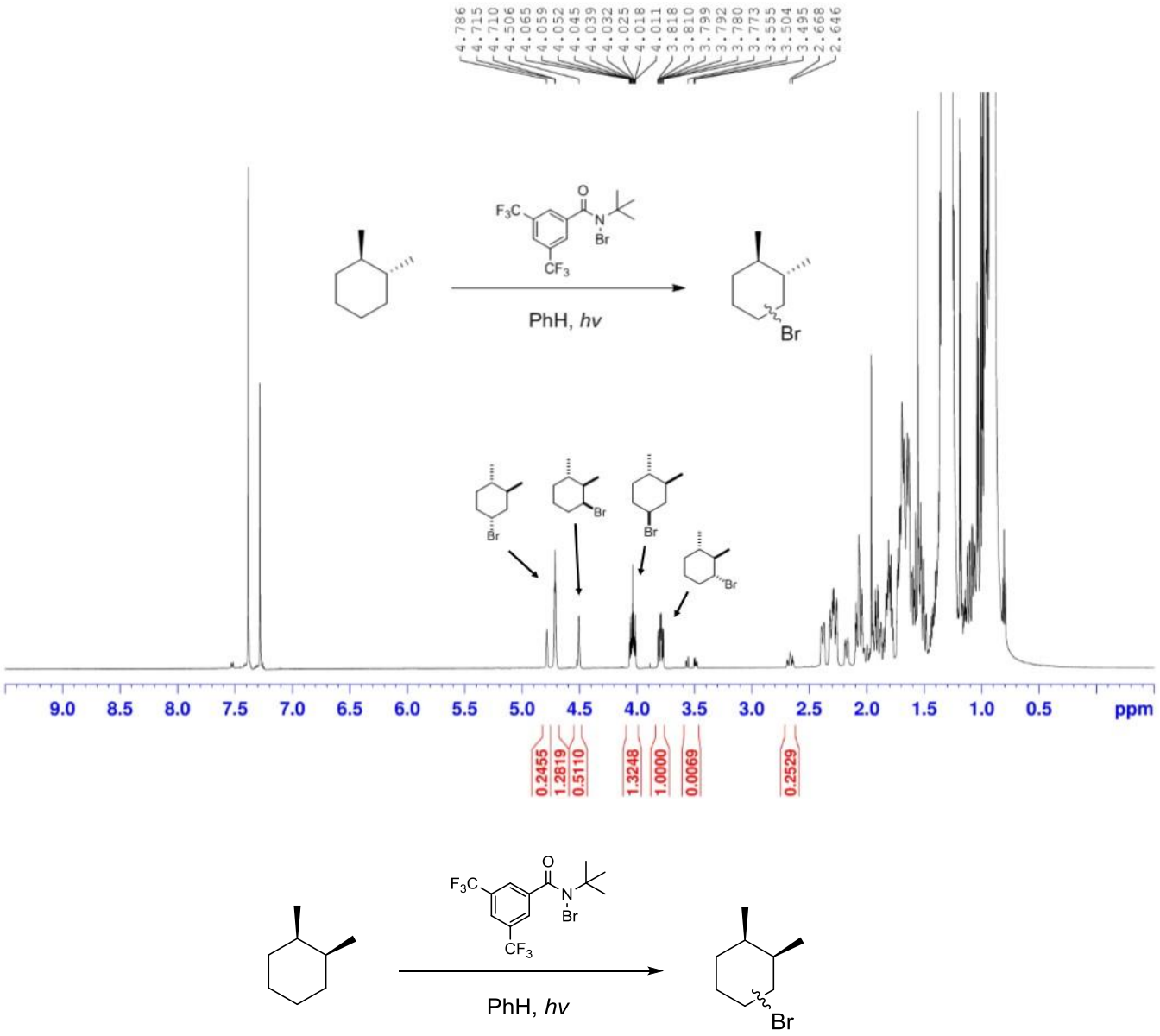


Figure 2-11. Crude NMR of bromination of *trans*-1,2-dimethylcyclohexane



1,2-*cis*-dimethylcyclohexane: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (45.0 mg, 0.114 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (300 μL). 1,2-*cis*-dimethylcyclohexane (11.1 μL, 0.076 mmol)

was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was run through a plug of silica and concentrated a second time. The reaction was analyzed by NMR using 2,5-dimethylfuran as an internal standard to determine the yield of secondary bromide products. GC analysis was used to determine the relative amount and yield, of the tertiary bromide products. 50.4% NMR yield of combined bromide products.

Figure 2-12. Gas chromatogram for bromination of *cis*-1,2-dimethylcyclohexane

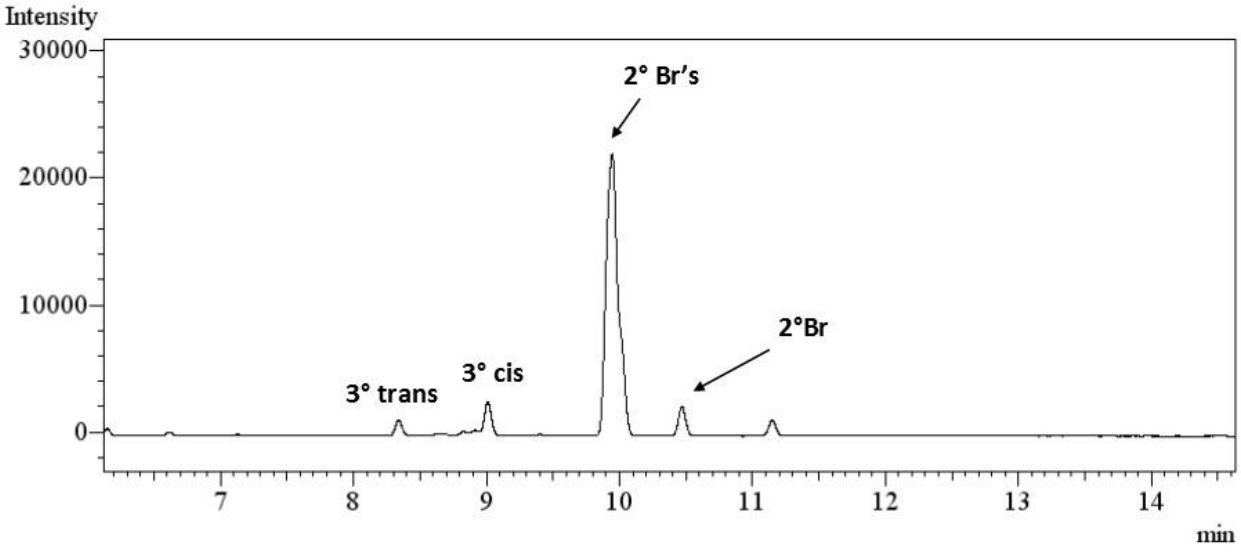


Figure 2-13. Overlaid gas chromatogram for bromination of *cis*-1,2-dimethylcyclohexane with authentic 3^o products

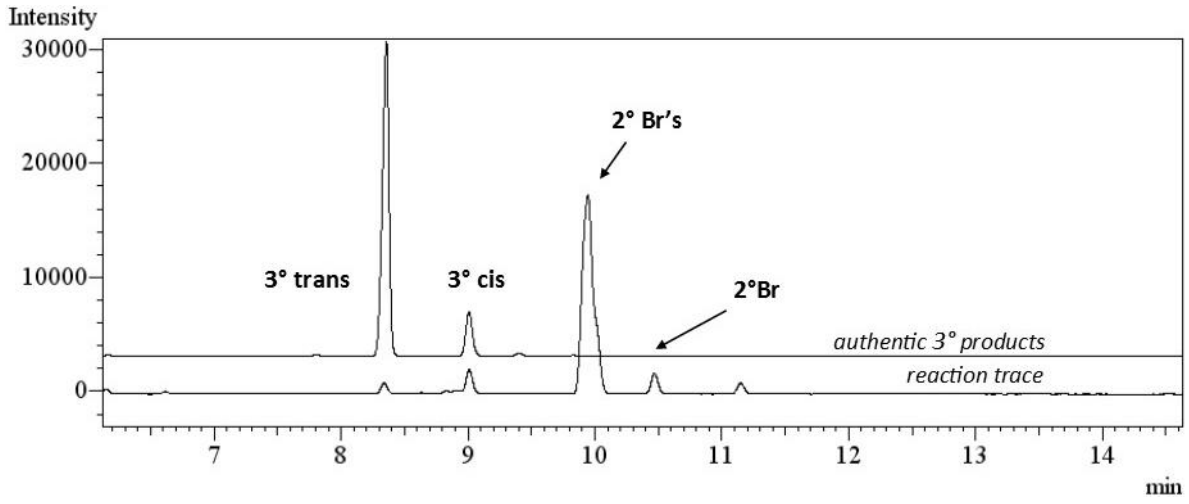
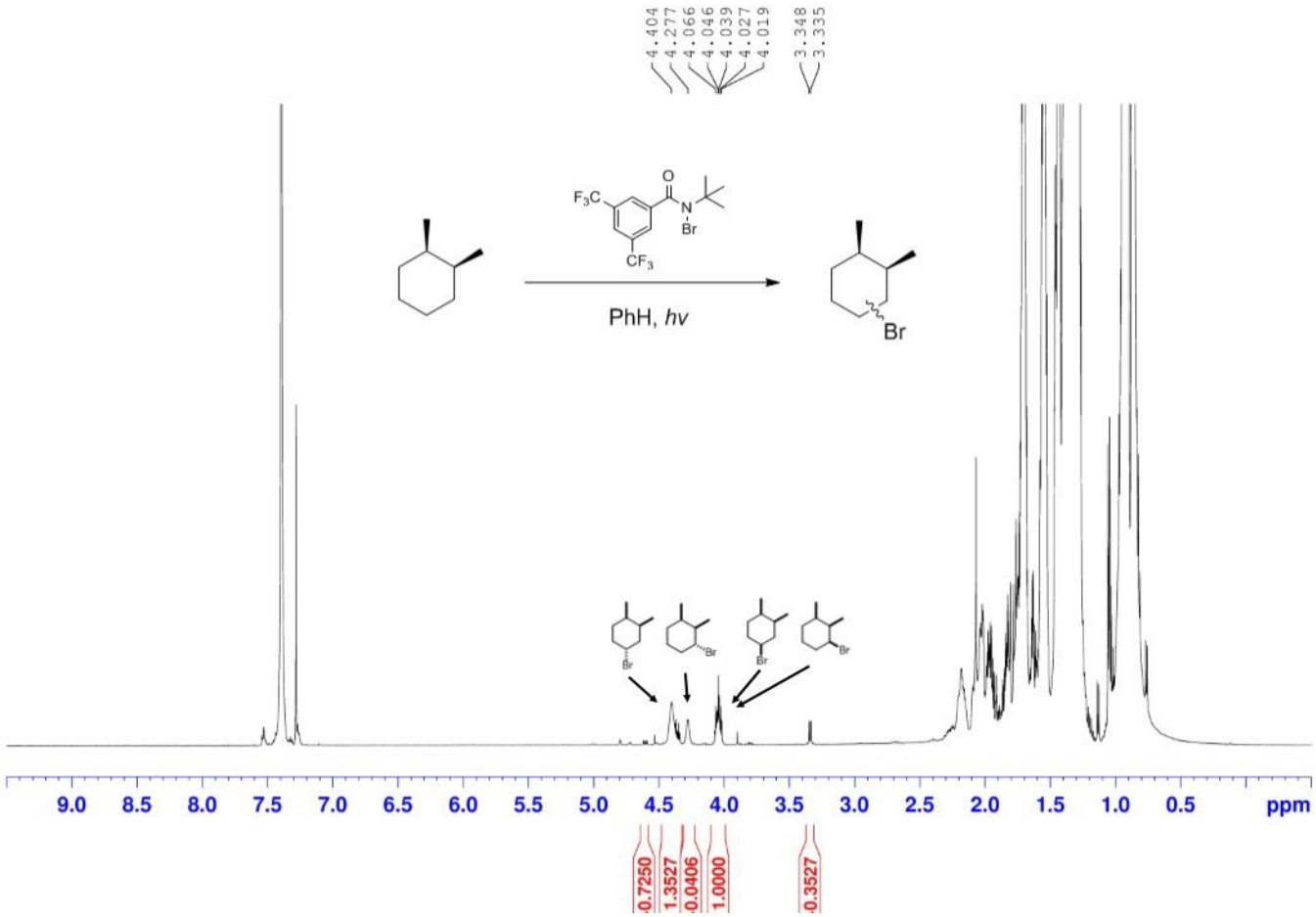
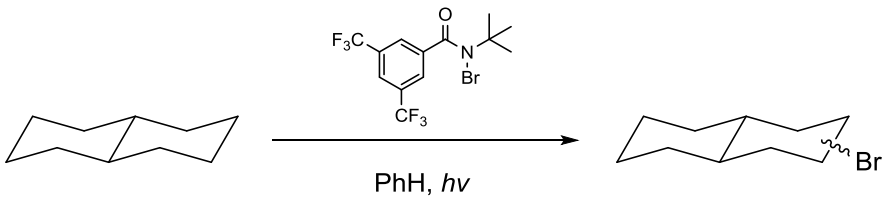


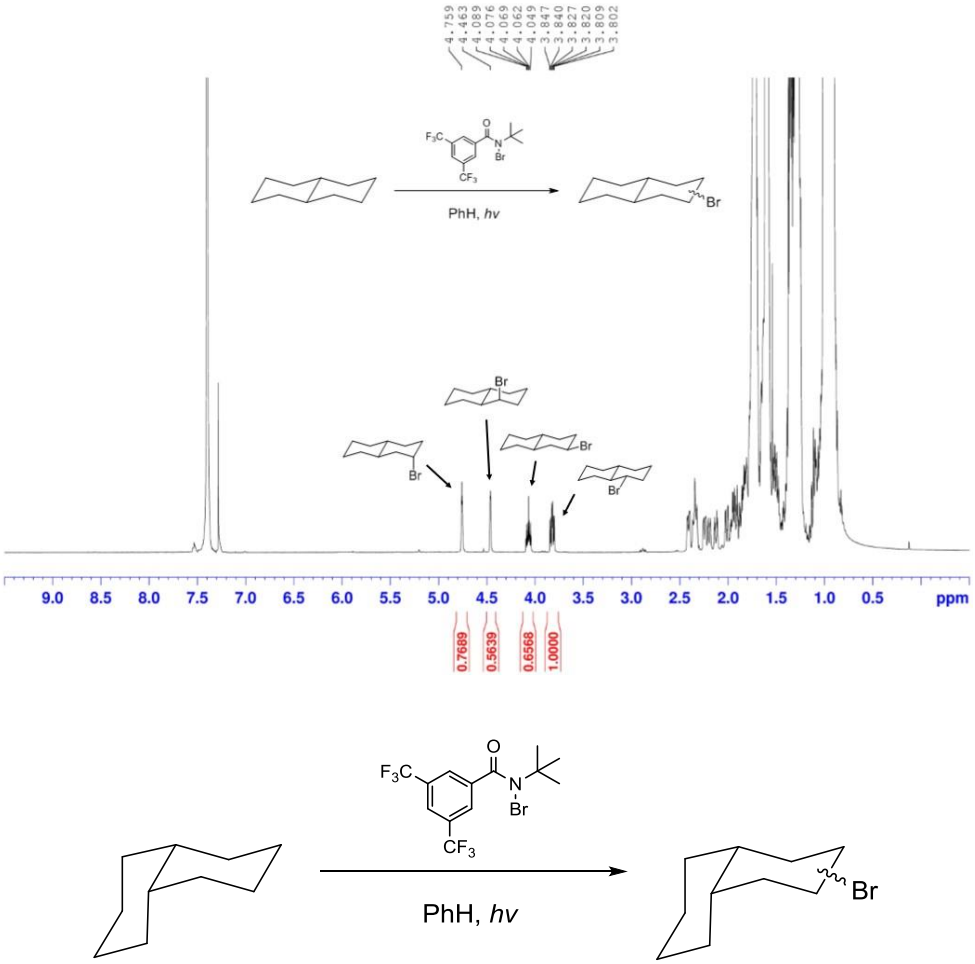
Figure 2-14. Crude NMR of reaction of *cis*-1,2 dimethylcyclohexane with reagent 6





***trans*-Decalin:** A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (45.0 mg, 0.114 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (400 μL). *trans*-Decalin (12.0 μL, 0.076 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was run through a plug of silica and concentrated a second time. The reaction was analyzed by NMR using 2,5-dimethylfuran as an internal standard to determine the yield of secondary bromide products. GC analysis was used to determine the relative amount and yield, of the tertiary bromide products.

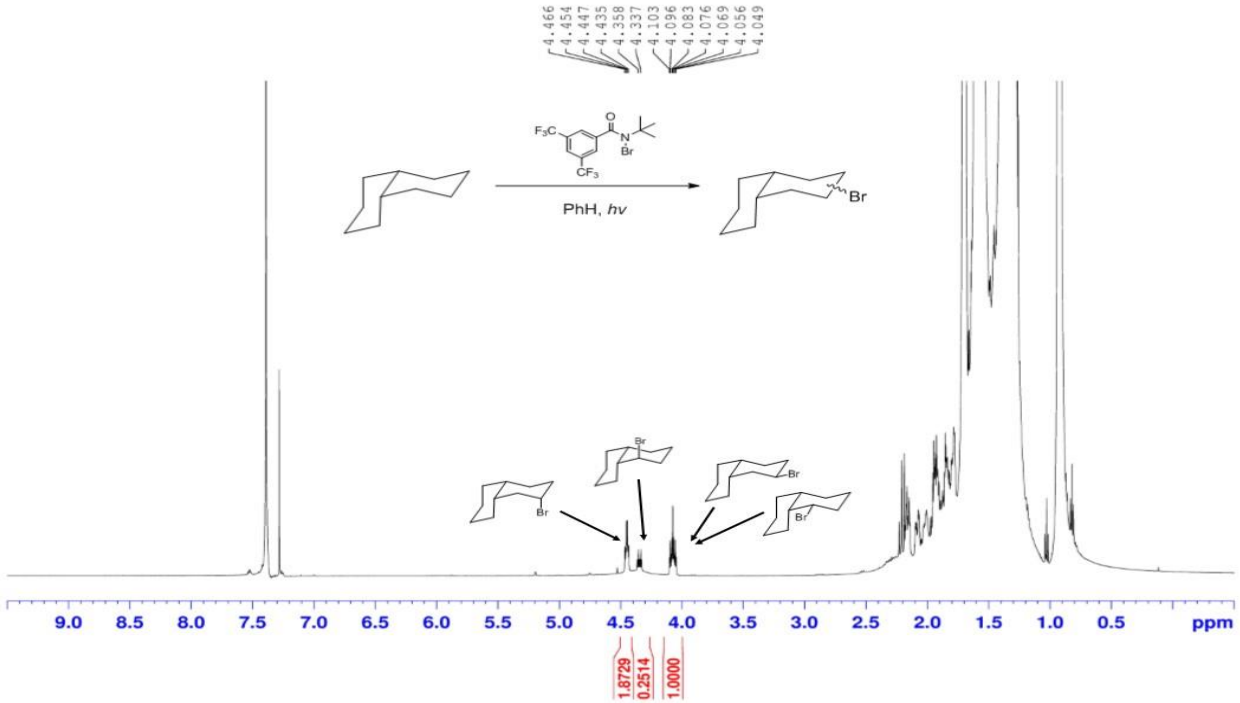
Figure 2-15. Crude NMR of reaction of *trans*-Decalin with reagent 6



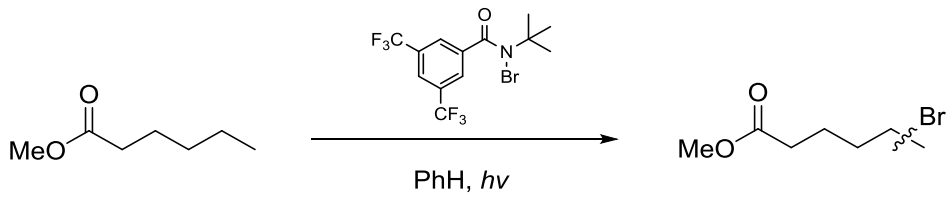
***cis*-Decalin:** A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (45.0 mg, 0.114 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (400 μL). *cis*-Decalin (12.0 μL, 0.076 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was run through a plug of silica and concentrated a second

time. The reaction was analyzed by NMR using 2,5-dimethylfuran as an internal standard to determine the yield of secondary bromide products. GC analysis was used to determine the relative amount and yield, of the tertiary bromide products. 55.0% GC yield of combined bromide products.

Figure 2-16. Crude NMR of bromination reaction of *cis*-Decalin with reagent 6



Bromination of Electron Withdrawing Alkanes



Methyl hexanoate: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-

thawed benzene (400 μL). Methyl hexanoate (3.5 μL, 0.025 mmol) was then added. *Note: alkane was added as a stock solution in benzene to improve the reproducibility of the results.* The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 56.1% GC yield of combined bromide products.

Figure 2-17. Gas chromatogram for bromination of methylhexanoate

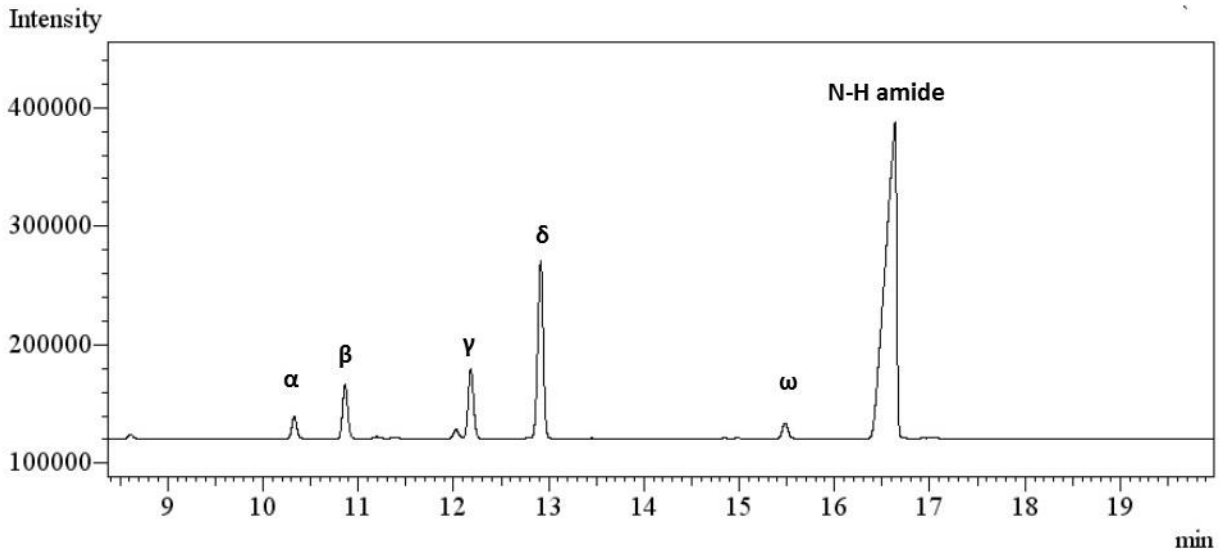


Figure 2-18. Overlaid gas chromatogram for bromination of methylhexanoate with authentic products

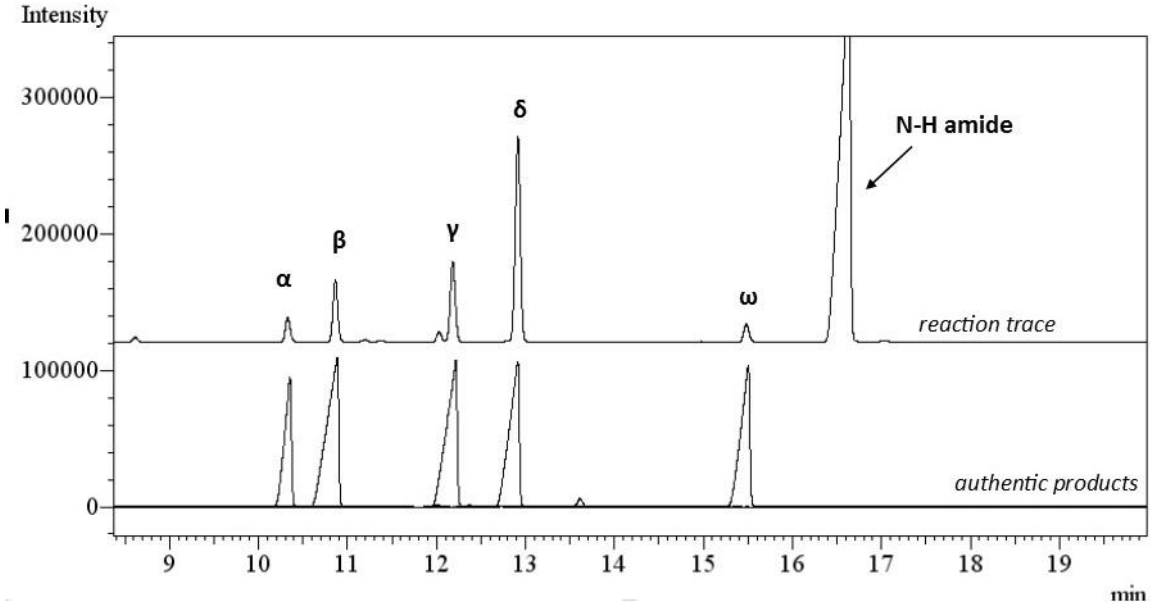
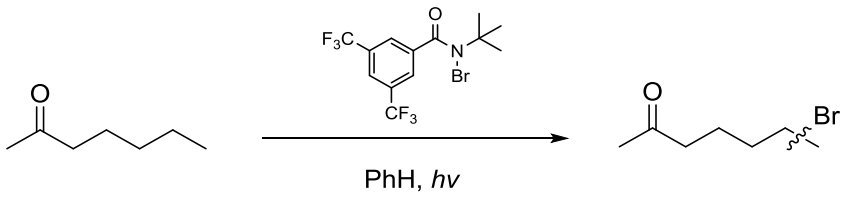


Table 2-11. Bromination of methylhexanoate with bromoamide 6

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	10.35	5.20
β	10.89	10.13
γ	12.21	18.10
δ	12.93	58.77
ω	15.52	7.78

The response factors for all isomers of bromo-Methylhexanoate were calculated to be nearly identical; therefore, the relative percent area of the product peaks reflects the relative amounts of the different isomers formed in the reaction.



2-Heptanone: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (400 μL). 2-Heptanone (3.6 μL, 0.025 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 72.3% GC yield of combined bromide products. *Only the major isomer was synthesized independently. The minor products were assigned in analogy to the bromination of methyl hexanoate.*

Figure S15. Overlaid gas chromatogram for bromination of 2-heptanone with authentic δ product

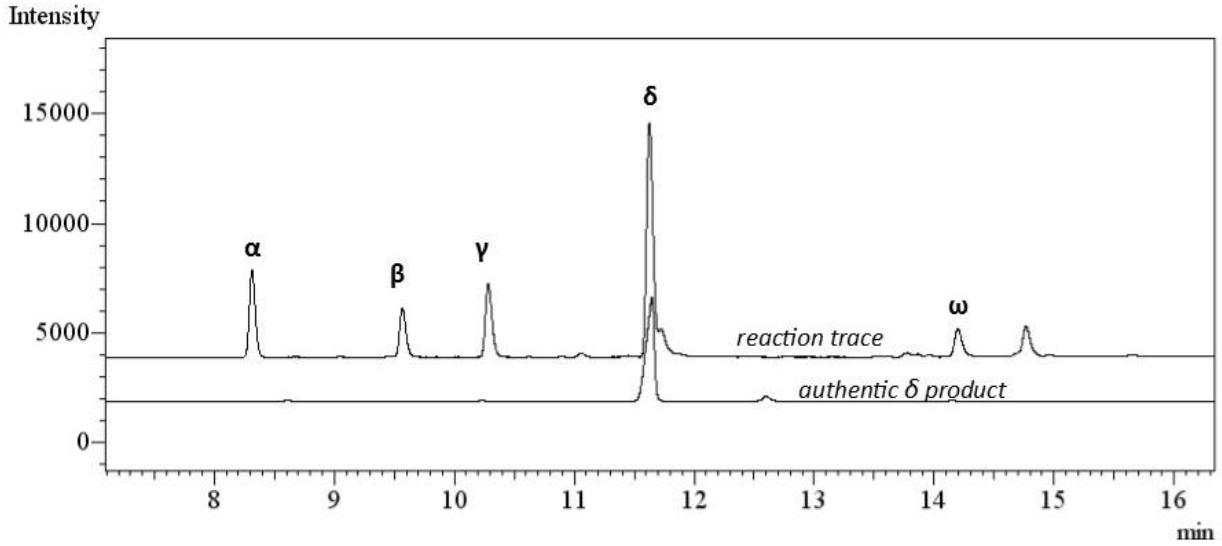
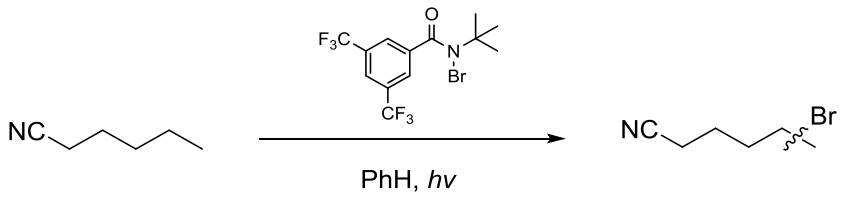


Table 2-12. Bromination of 2-heptanone with bromoimide 6

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	8.32	13.28
β	9.58	8.31
γ	10.30	16.22
δ	11.65	53.79
ω	14.21	8.43



Hexanenitrile: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (400 μL). Hexanenitrile (3.0 μL, 0.025 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 49.8% GC yield of combined bromide products. *Only the major isomer was synthesized independently. The minor products were assigned in analogy to the bromination of methyl hexanoate.*

Figure 2-19. Overlaid chromatogram of bromination of hexanenitrile with authentic δ product

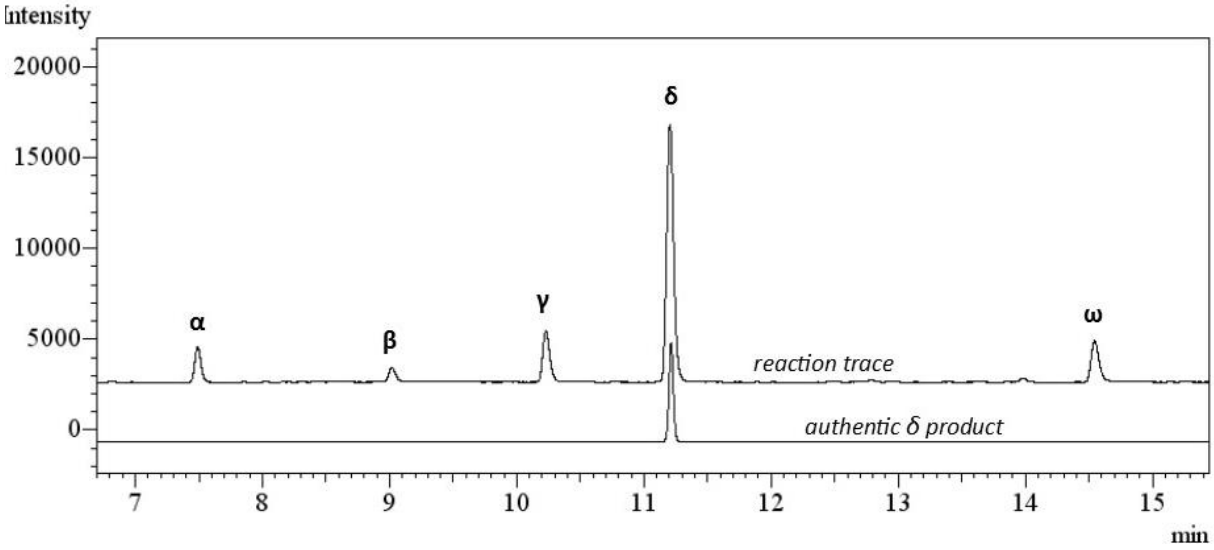
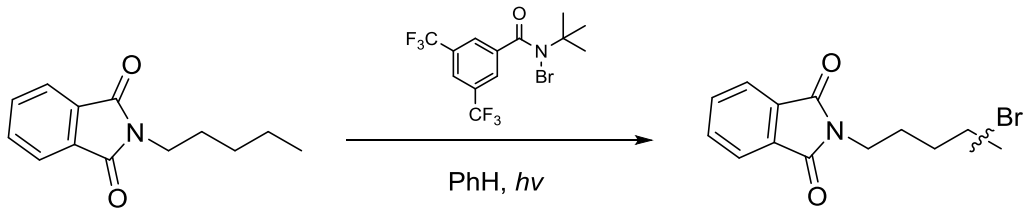


Table 2-13. Bromination of hexanenitrile

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	7.51	3.21
β	9.03	2.70
γ	10.25	11.64
δ	11.23	68.33
ω	14.56	14.19



N-Penthylphthalimide: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-

pump-thawed benzene (400 μL). *N*-Pentylphthalimide (5.4 mg, 0.025 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 56.4% GC yield of combined bromide products.

Only the major isomer was synthesized independently. The minor products were assigned in analogy to the bromination of methyl hexanoate.

Figure 2-20. Overlaid gas chromatogram for bromination of *N*-pentylphthalimide with authentic δ product

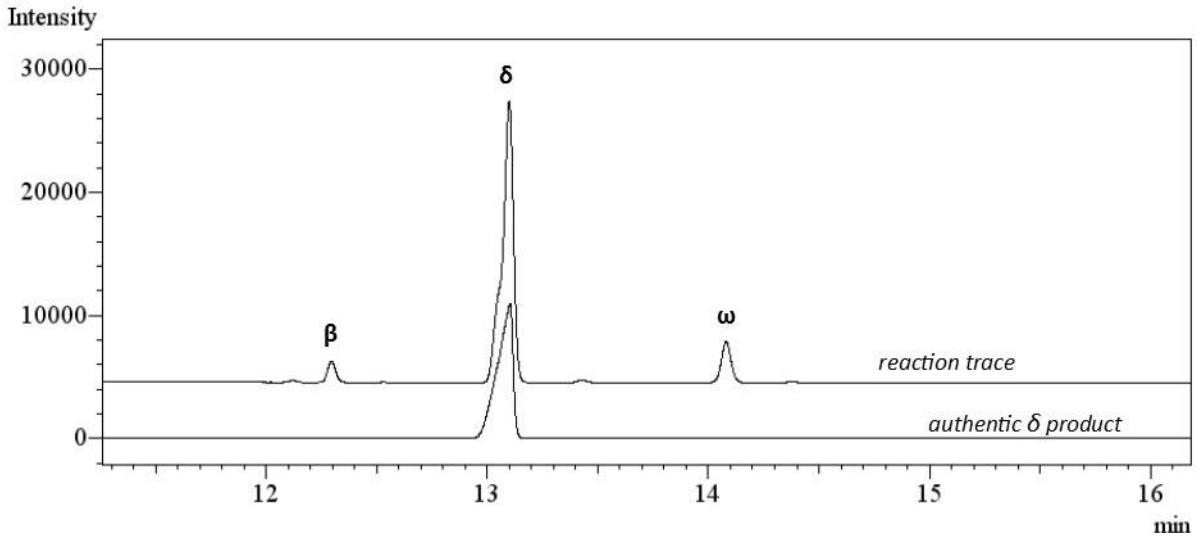


Table 2-14. Bromination of *N*-pentylphthalimide with reagent 6

Chromatograph Data Selectivity		
Product	Retention Time	Percent Area
α	----	----
β	----	----
γ	11.99	6.52
δ	13.14	81.74
ω	14.84	11.69

OTFA-Pentanol: A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (40.0 mg,0.102 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (400 μL). *OTFA*-Pentanol (9.3 mg, 0.051 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 73.1% GC yield of combined bromide products. *Only the major isomer was synthesized independently. The minor products were assigned in analogy to the bromination of methyl hexanoate.*

Figure 2-21. Overlaid chromatogram for bromination of OTFA-pentanol with authentic δ product

Figure 2-22. Gas chromatogram for bromination of cyclohexylphthalimide

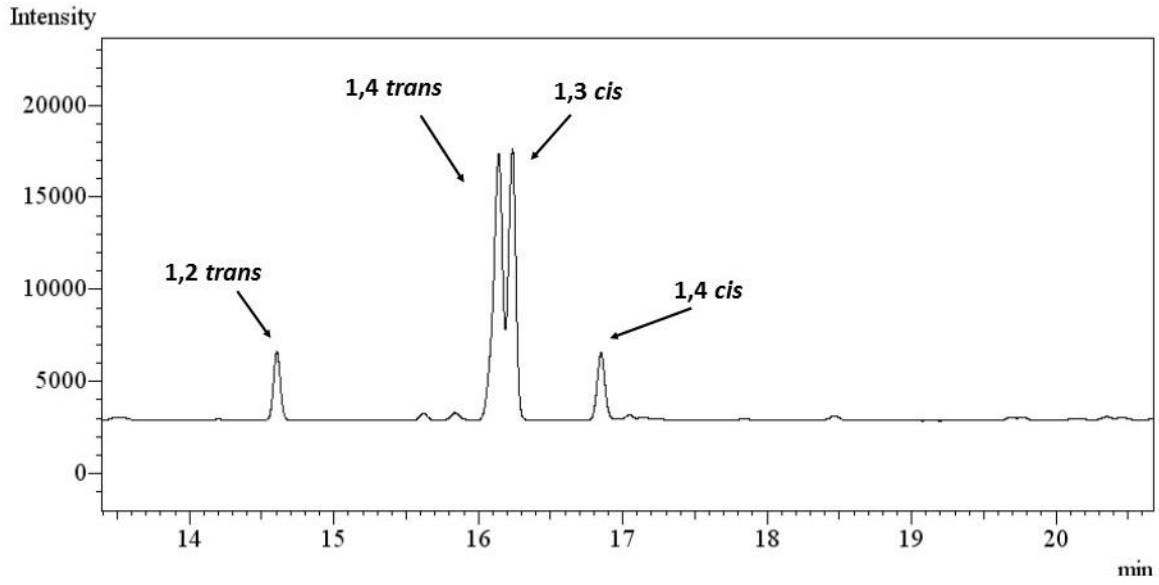


Figure 2-23. Overlaid chromatogram for bromination of cyclohexylphthalimide with authentic products

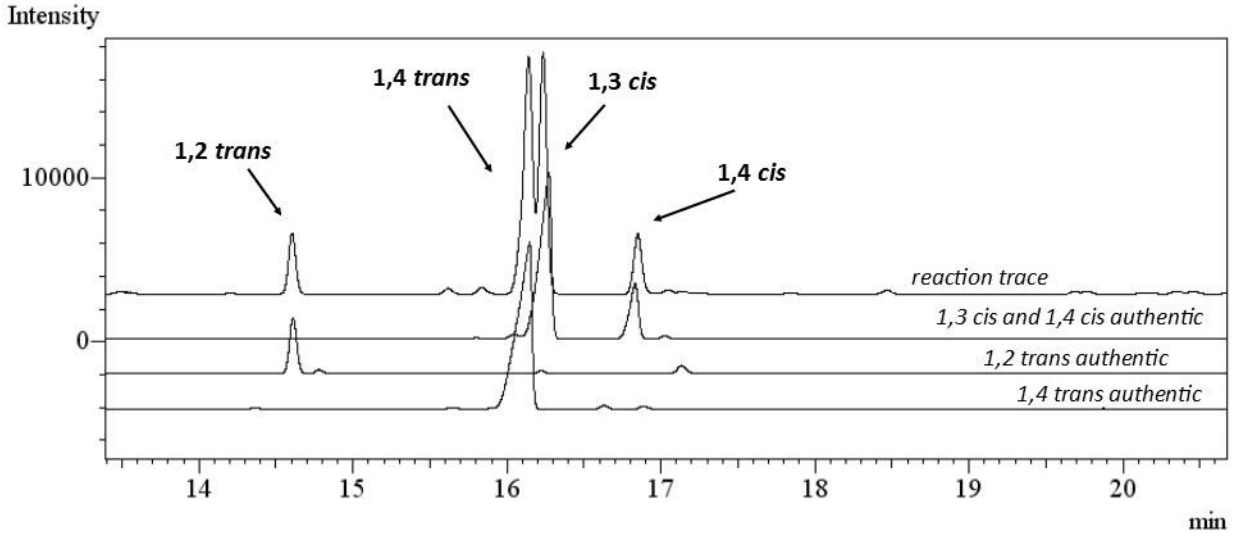
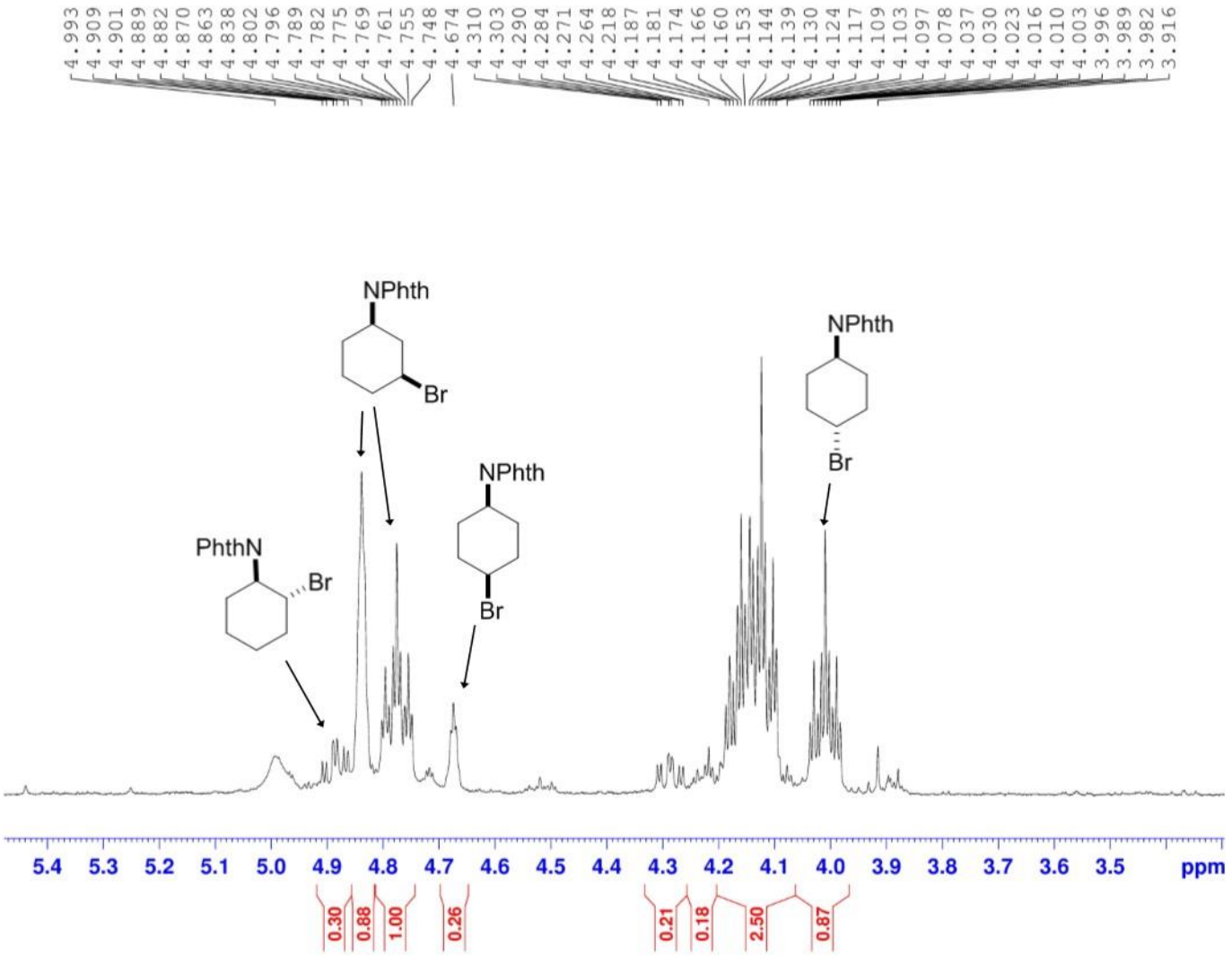


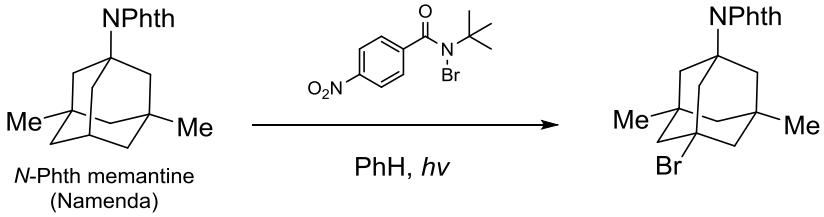
Table 2-15. Bromination of *N*-cyclohexylphthalimide with reagent 6

Chromatograph Data Selectivity		
Product	Retention Time	Percent Area
1,2-*trans*	14.60	8.47
1,3-*cis*	16.14	45.39
1,4-*trans*	16.23	36.62
1,4-*cis*	16.85	9.51

Figure 2-24. Crude NMR of Reaction of Cyclohexylphthalimide with Reagent 6



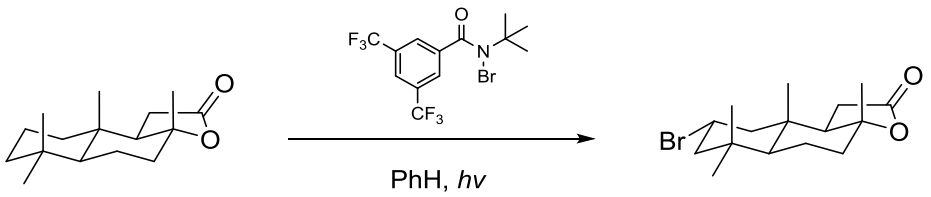
Bromination of Complex Substrates



Namenda: A flame-dried, 1 dram vial was charged with a stir bar and fitted with a PTFE lined screw cap. Bromoamide (45 mg, 0.15 mmol) was added to the vial in the absence of ambient light,

and the reaction was taken into a glovebox, and dissolved in 450 uL of dry, freeze-pump-thawed benzene. N-Phth memantine (16.1 mg, 0.05 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with 2x 100w tungsten filament light bulbs for 8 hours. When the reaction was complete it was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was filtered through cotton and concentrated a second time. The crude reaction mixture was purified using column chromatography eluting with 1% - 5% EtOAc in Hexanes to give the product (13.6 mg, 70%) as a white solid. Some of the unreacted substrate was isolated with the product and proved to be inseparable. The NMR yield from the crude reaction mixture (trimethoxybenzene as an internal standard) was 82%.

Analytical Data for **36:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.84 - 7.75 (m, 2 H), 7.74 - 7.67 (m, 2 H), 2.96 (s, 2 H), 2.26 (d, *J* = 13.6 Hz, 3 H), 2.20 - 2.07 (m, 6 H), 1.99 (d, *J* = 11.7 Hz, 3 H), 1.45 - 1.35 (m, 2 H), 0.99 (s, 6 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) □ = 169.4, 133.9, 131.7, 122.7, 62.8, 62.3, 53.8, 49.1, 48.6, 44.4, 35.9, 29.9, 29.7, 29.3 ppm; **IR** (thin film, cm^{-1}) 1771.3, 1710.5, 1530.2, 1456.9, 1347.0, 1315.2, 1264.1, 1113.7, 873.6, 717.4; **HRMS** (ESI) Calcd. for $[C_{20}H_{22}BrNO_2+H]^+$ = 388.08, Found = 388.10



Sclareolide: A flame-dried, 1 dram vial was charged with a stir bar and fitted with a PTFE lined screw cap. Bromoamide (152.4 mg, 0.390 mmol) was added to the vial in the absence of ambient light, and the reaction was taken into a glovebox, and dissolved in 1.2 mL of dry, freeze-pump-

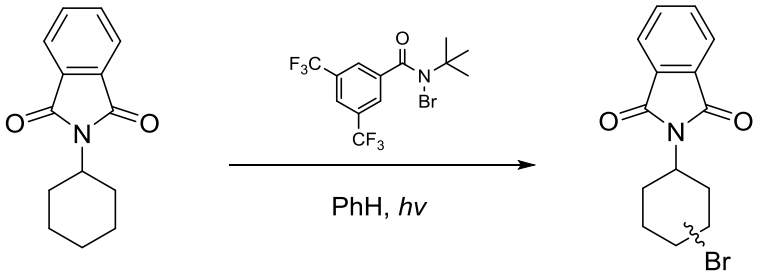
thawed benzene. Sclareolide (27.9 mg, 0.111 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 8 hours. When the reaction was complete it was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was filtered through cotton and concentrated a second time. The crude reaction mixture was purified using column chromatography eluting with 5% - 10% EtOAc in Hexanes to give the product (24.4 mg, 67%) as a white solid. The NMR yield from the crude reaction mixture (1,3,5-trimethoxybenzene as an internal standard) was 79%. The analytical data was consistent with the literature.[43]

Analytical Data for **38:** **^{1}H NMR** (600 MHz, CHLOROFORM-d) δ= 4.39 (tt, J= 12.4, 4.1 Hz, 1H), 2.42 (t, J= 16.2, 14.7 Hz, 1H), 2.27 (dd, J = 16.2, 6.5 Hz, 1H), 2.18 – 2.06 (m, 3H), 2.02 (dd, J= 14.7, 6.5 Hz, 1H), 1.89 (dq, J = 14.3, 3.4 Hz, 1H), 1.80 – 1.63 (m, 2H), 1.60 – 1.51 (m, 1H), 1.43 – 1.28 (m, 4H), 1.16 (dd, J = 12.7, 2.7 Hz, 1H), 0.96 (s, 6H), 0.89 (s, 3H).

^{13}C NMR (125 MHz, CHLOROFORM-d) δ = 175.93, 85.75, 58.49, 55.63, 53.29, 50.65, 45.81, 38.97, 38.36, 36.72, 32.82, 28.55, 21.61, 21.20, 20.22, 15.60; **IR** (thin film, cm^{-1}) 1771.9, 1448.6, 1395.1, 1262.0, 1132.4, 857.2, 723.5; **HRMS** (ESI) Calcd. for $[C_{16}H_{25}BrO_2+H]^+$ = 329.10, Found = 329.12

Table 2-16. Bromination of OTFA pentanol with bromoimide 6

Bromination of OTFA Pentanol: Selectivity		
Product	Retention Time	Percent Area
α	----	----
β	5.18	3.61
γ	6.31	13.41
δ	7.17	66.58
ω	9.81	16.40



***N*-Cyclohexylphthalimide:** A flame-dried, 1 dram vial was charged with a stir bar and. bromoamide **6** (20.0 mg, 0.051 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (400 μL). *N*-Cyclohexylphthalimide (6.0 mg, 0.025 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with two 100W tungsten filament lightbulbs for 4 hours. Upon completetion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 61.3% yield of combined bromide products.

Figure 2-25. Gas chromatogram for bromination of cyclohexylphthalimide

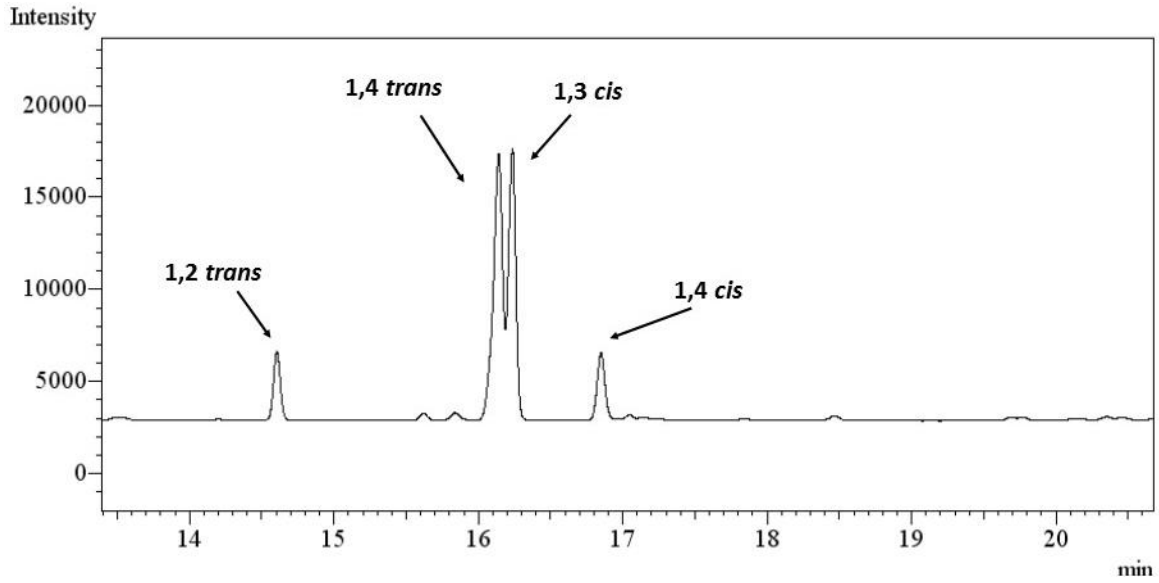


Figure 2-26. Overlaid chromatogram for bromination of cyclohexylphthalimide with authentic products

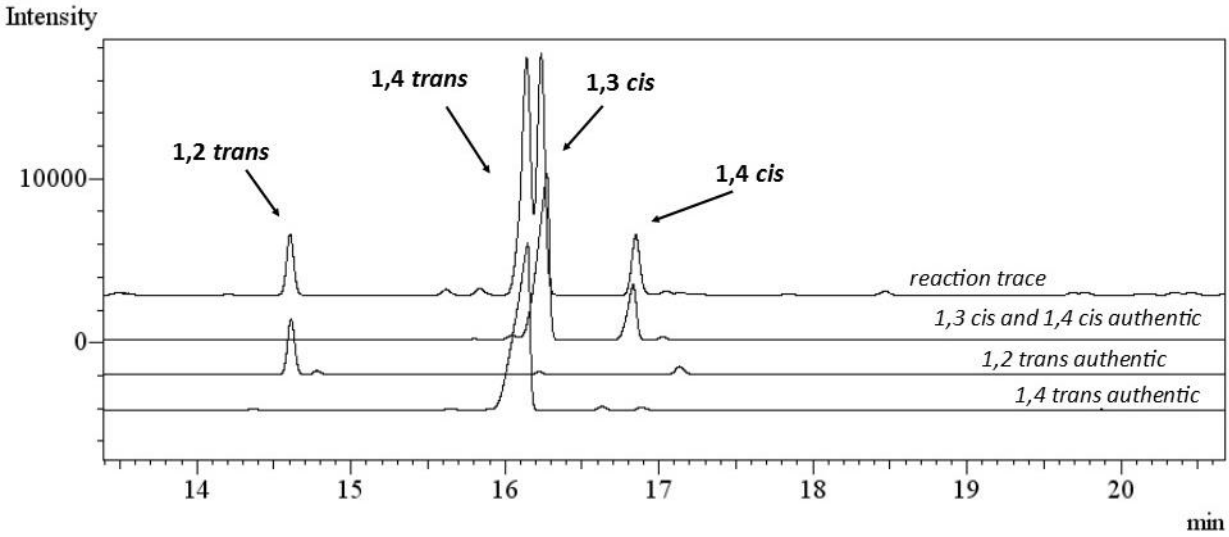
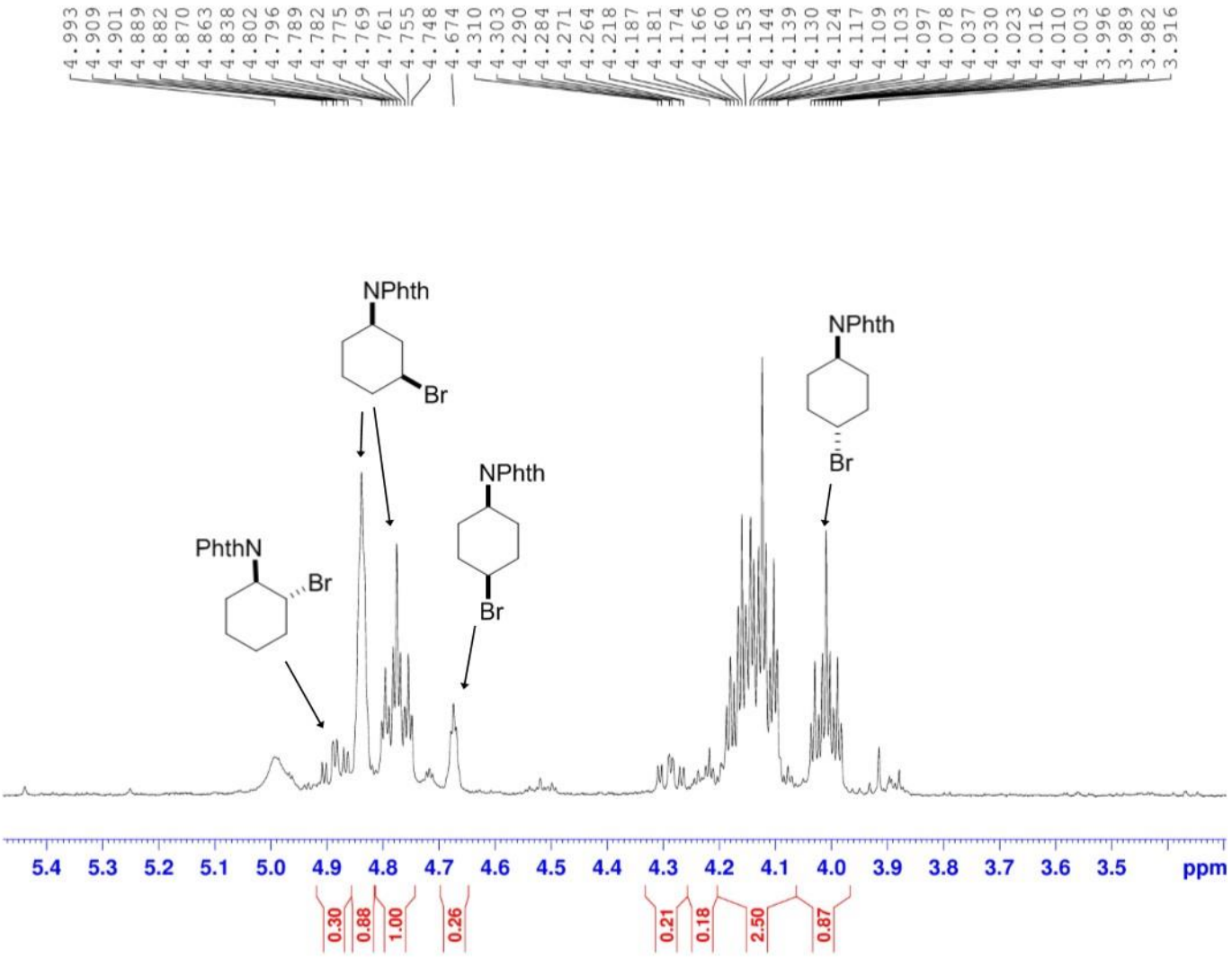


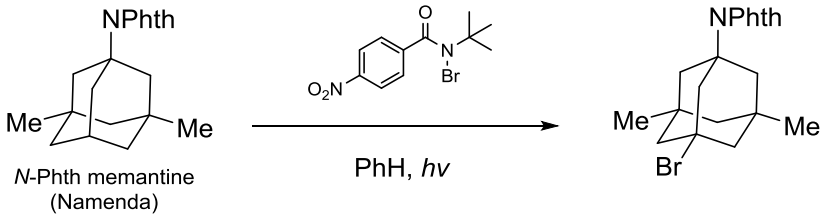
Table 2-17. Bromination of *N*-cyclohexylphthalimide with reagent 6

Chromatograph Data Selectivity		
Product	Retention Time	Percent Area
1,2-*trans*	14.60	8.47
1,3-*cis*	16.14	45.39
1,4-*trans*	16.23	36.62
1,4-*cis*	16.85	9.51

Figure 2-27. Crude NMR of reaction of cyclohexylphthalimide with reagent 6

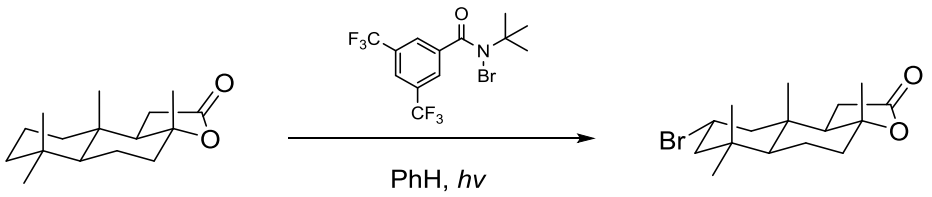


Bromination of Complex Substrates



Namenda: A flame-dried, 1 dram vial was charged with a stir bar and fitted with a PTFE lined screw cap. Bromoamide (45 mg, 0.15 mmol) was added to the vial in the absence of ambient light, and the reaction was taken into a glovebox, and dissolved in 450 uL of dry, freeze-pump-thawed benzene. N-Phth memantine (16.1 mg, 0.05 mmol) was then added. The reaction was then sealed with teflon tape and taken out of the glovebox, and placed in a circulating cooling bath (roughly room temperature) and irradiated with 2x 100w tungsten filament light bulbs for 8 hours. When the reaction was complete it was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was filtered through cotton and concentrated a second time. The crude reaction mixture was purified using column chromatography eluting with 1% - 5% EtOAc in Hexanes to give the product (13.6 mg, 70%) as a white solid. Some of the unreacted substrate was isolated with the product and proved to be inseparable. The NMR yield from the crude reaction mixture (trimethoxybenzene as an internal standard) was 82%.

Analytical Data for **36: ^{1}H NMR** (600MHz ,CHLOROFORM-d) □ = 7.84 - 7.75 (m, 2 H), 7.74 - 7.67 (m, 2 H), 2.96 (s, 2 H), 2.26 (d, *J* = 13.6 Hz, 3 H), 2.20 - 2.07 (m, 6 H), 1.99 (d, *J* = 11.7 Hz, 3 H), 1.45 - 1.35 (m, 2 H), 0.99 (s, 6 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) □ = 169.4, 133.9, 131.7, 122.7, 62.8, 62.3, 53.8, 49.1, 48.6, 44.4, 35.9, 29.9, 29.7, 29.3 ppm; **IR** (thin film, cm^{-1}) 1771.3, 1710.5, 1530.2, 1456.9, 1347.0, 1315.2, 1264.1, 1113.7, 873.6, 717.4; **HRMS** (ESI) Calcd. for $[C_{20}H_{22}BrNO_2+H]^+$ = 388.08, Found = 388.10



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^{13}C NMR (125 MHz, CHLOROFORM-d) δ = 175.93, 85.75, 58.49, 55.63, 53.29, 50.65, 45.81, 38.97, 38.36, 36.72, 32.82, 28.55, 21.61, 21.20, 20.22, 15.60; **IR** (thin film, cm^{-1}) 1771.9, 1448.6, 1395.1, 1262.0, 1132.4, 857.2, 723.5; **HRMS** (ESI) Calcd. for $[C_{16}H_{25}BrO_2+H]^+$ = 329.10, Found = 329.10

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(39) Dauben, WG; Bridon, DP; Kowalczyk, BA. *J. Org. Chem.* **1989,** *54*, 6101.

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3. CHAPTER THREE

Aliphatic C-H Chlorination Using *N*-Chloroamides

3.1 Introduction

Reactions that selectively convert C-H bonds to C-C or C-heteroatom bonds have the power to dramatically change the way synthetic chemists prepare small molecules. While it is a goal to continue to develop C-H transformations with improved site-selectivity, it is equally as important to expand the number of different C-H transformations – to expand the synthetic toolbox. The development of selective aliphatic C-H chlorination technologies will nicely compliment C-H bromination protocols owing to differing reactivity of the alkyl bromide products formed in the reaction. The free radical chlorination of unactivated alkanes with elemental chlorine is industrially important for the preparation of a number of chlorinated small molecules.[1] The vast majority of these applications involve hydrocarbons with only one type of C−H bond. This is a consequence of the promiscuity of the chlorine free radical, which leads to poor site selectivities and a proclivity for undesired polyhalogenations with more complex substrates.[2] C-H chlorination reactions with improved selectivities are required for such applications. Alkyl chlorides are highly useful synthetic building blocks; amine alkylation of alkyl halides is one of the most common reactions in industry, and >2000 chlorine-containing natural products have been identified to date.[3] New methods for practical, selective aliphatic C−H chlorinations hold significant potential for streamlining the synthesis and derivatization of broad classes of synthetically and medicinally valuable small molecules

3.2 Background

Alkane chlorination was one of the first C-H functionalization methods reported, though little work has been done since to improve on the initial methods. Alkane chlorination is the conversion of an aliphatic sp^3 C-H bond into a C-Br bond resulting in an alkyl chloride product. See **Chapter 1.2.2** for an overview of alkane chlorination methods.

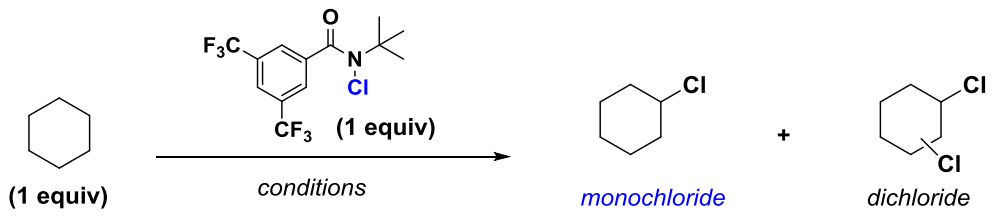
3.3 Reaction Development

We previously reported the development of a set of easily accessed, bench stable N-bromoamides for the siteselective, intermolecular bromination of unactivated C−H bonds (see **Chapter 2)**. These reactions used substrate as the limiting reagent and delivered products using elements of both steric and electronic control.[4] We sought to extend our approach to C−H chlorination using household lamp irradiation and *N*-chloroamides that are trivially prepared from amides and NaOCl. Our studies have shown that in contrast to the C−H bromination disclosed in **Chapter 2**, background reactions were significant in these studies. We have developed a simple protocol that overcomes this undesired background reactivity. We have also demonstrated the unique site and chemoselectivities of our aliphatic C−H chlorination, including applications to substrates containing more reactive tertiary, allylic, or benzylic C−H bonds. Unsaturated substrates are rare in studies of intermolecular aliphatic C−H functionalization and are a notable aspect of this approach.[5] Finally, we demonstrate the practical utility of our chlorination method in the short synthesis of the potent cytotoxin *chlorolissoclimide* and analogues, wherein gram-scale, highly selective monochlorination of sclareolide plays a pivotal role.

3.3.1 Initial Studies

In our initial attempts to affect an aliphatic C-H chlorination we synthesized the *N*-chlorinated analogue of *N*-bromoamide 6 that was identified in **Chapter 2** to perform in the C-H functionalization reaction with the greatest steric selectivity, electronic selectivity, and reaction efficiency. Under identical optimized reaction conditions from the bromination system, however, the selectivity of our initial system was not preserved using the N-chloroamide reagent. The cyclohexane chlorination using N-chloroamide 1 (**Table 3-1**, entry 1) provided a significant

Table 3-1. Chlorination of cyclohexane under various conditions[a]



entry	reagents	% Mono-Cl	% Di-Cl	% Conversion
1	chloroamide **1** PhH, *hv*, RT	86.0	14.0	46.1
2	chloroamide **1** PhH, Benzoyl Peroxide, 65°	86.0	14.0	46.1
3	chloroamide **1** PhH, *hv*, 1 equiv Cs_2CO_3, 55°	96.9	3.1	67.9
4	NCS, AIBN, 60°	71.1	28.9	N/A
5	SO_2Cl_2 (1 equiv); Benzoyl Peroxide, 85° in PhH	71.1	28.9	85.7
6	Mn(TPP)Cl/NaOCl	89.9	10.1	62.3

[a]Reactions were performed in PhH at T°C specified under Ar using visible light irradiation with 1 equiv of substrate and N-chloroamide (or other chlorinating agent). Yields were determined by GC analysis.

amount of dichloride products. Initiation using benzoyl peroxide (BPO) instead of visible light was also suboptimal. At this stage, we hypothesized that the promiscuity of the chlorine radical could be adversely affecting our reaction selectivity. This idea is supported by the prior studies of

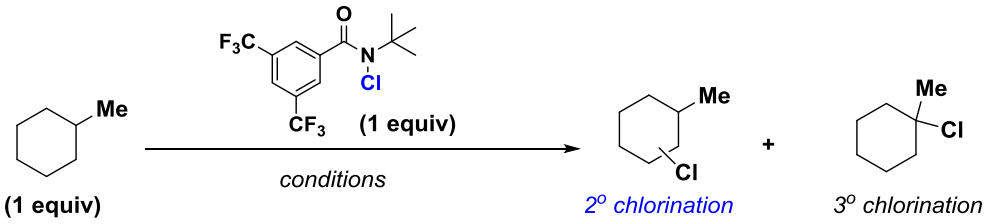
Greene, who demonstrated that the chain carrying species of aliphatic C−H chlorinations with N-chloroamides can vary widely depending upon the exact reaction conditions.[6] Specifically, we questioned whether trace acid was reacting with reagent 1 to deliver amide and Cl_2. Adding 1 equiv of Cs_2CO_3 improved the selectivity for monochlorination (90.5%) using both light and BPO initiation, supporting this hypothesis (**Table 3-1**, entry 3). We hypothesize that increasing the reaction temperature to 55 °C is required for a selectivity of 96.9% monochlorination, owing to greater solubility. A survey of classical C−H chlorinations demonstrated either low reactivity with N-chlorosuccinimide or uncontrolled reactivity with SO_2Cl_2 (**Table 3-1**, entries 4 and 5). Chlorination using a biomimetic Mn−porphyrin system provided good conversion; however, a significant amount of dichlorination product was formed (**Table 3-1**, entry). The selectivity achieved in the initial reaction development is promising, as C-H chlorination methods using substrate as the limiting reagent are extremely rare.[7]

3.3.2 Substrate Scope – Steric Selectivity

Our studies continued with an investigation of the sterically dictated site selectivities of our C−H chlorination using methylcyclohexane as substrate (**Table 3-2**). As observed in the reactions of cyclohexane in **Table 3-1**, chlorination using N-chloroamide 1 in the absence of base provides suboptimal selectivities, likely owing to background reactions involving Cl_2 and the chlorine free radical. The addition of 10 mol % amylene, a known Cl_2 scavenger,[8] greatly favors methylene functionalization (97.7%, $k_{secondary}/k_{tertiary}$, k_s/k_t = 4.2), albeit at low conversion (**Table 3-2,** entry 2). We found that added base could serve a similar role without decreasing conversion, with a higher yield at 55 °C (**Table 3-2,** entries 3 and 4). We also surveyed the secondary (desired) versus tertiary (undesired) selectivity using known chlorination methods. Classical methods involving either N-chlorosuccinimide or sulfuryl chloride provided modest selectivities (k_s/k_t, =

0.31 and 0.28, respectively) after correcting for the number of tertiary (one) and secondary (ten) sites available (**Table 3-2,** entries 6 and 7).[9] Chlorination catalyzed by Mn(TPP)Cl provided similar selectivity (ks/kt = 0.38). The high level of secondary selectivity in this functionalization of a simple cyclic hydrocarbon is higher than any known system for aliphatic C−H chlorination.

Table 3-2. Chlorination of methylcyclohexane under various conditions[a]



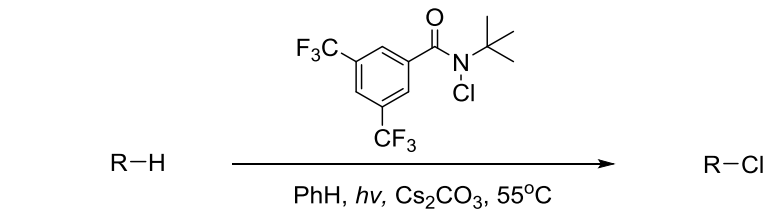
entry	reagents	% 2° Cl	% 3° Cl	$k_{secondary}/k_{tertiary}$	
1	chloroamide **1** PhH, *hv*	74.5	25.5	0.29	
2	chloroamide **1** PhH, BPO, 10% amylene, 55°	97.7	2.3	4.23	**(<5% yield)**
3	chloroamide **1** PhH, BPO, 1 equiv Cs_2CO_3, 55°	98.1	1.9	5.16	**(68% yield)**
4	chloroamide **1** PhH, *hv*, 1 equiv Cs_2CO_3, 55°	98.1	1.9	5.16	**(74% yield)**
5	Mn(TTP)Cl/NaOCl	89.9	10.1	0.28	
6	SO_2Cl_2; BPO, 85° in PhH	73.9	26.1	0.28	
7	NCS, AIBN, 60°	71.1	28.1	0.28	

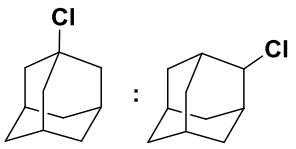
[a]Reactions were performed in PhH at T°C specified under Ar using visible light irradiation with 1 equiv of substrate and N-chloroamide. Yields were determined by GC analysis.

We extended our steric selectivity studies to additional hydrocarbon substrates such as norbornane, which under our standard chlorination conditions delivered a 54% yield of 2-exo-chloronorbornane as a single product (**Table 3-3**, entry 3). As comparison, the C−H chlorination of norbornane with common reagents (e.g., Cl_2 or SO_2Cl_2) leads to mixtures of the *exo* and *endo* isomers. Both *trans*- and *cis*-1,2-dimethyl cyclohexanes benchmark substrates for sterically selective aliphatic C−H functionalizations -exhibited excellent methylene selectivity (**Table 3-3**,

entries 2 and 4).[10] Adamantane C−H chlorination involving the chlorine free radical is documented to be a poorly selective process, with kt/ks = 3.5.[11] Reaction of adamantane under our standard reaction conditions furnished the two regioisomers in a 19:1 ratio (kt/ks = 57), favoring functionalization of the less hindered tertiary site, and highlighting the unique selectivity profile of the current system.

Table 3-3. Sterically selective chlorination of diverse hydrocarbon substrates[a]

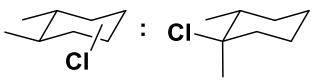




(36:1) 69% yield

adamantane

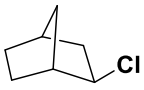
(1)



(>99:1) 79% yield

1,2-trans dimethyl cyclohexane

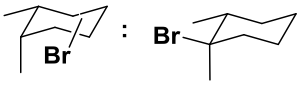
(2)



exo:endo
(>99:1) 54%

norbornane

(3)



(11:1) 73% yield

1,2-cis dimethyl cyclohexane

(4)

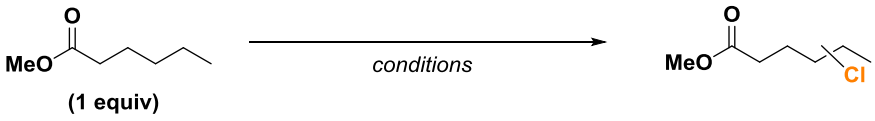
[a]Reactions were performed in PhH at 55° under Ar using visible light irradiation with 1 equiv of substrate and N-chloroamide. Yields were determined by GC or NMR analysis.

3.3.3 Substrate Scope- Electronic Selectivity

Next we surveyed the potential to achieve an electronically site-selective C−H chlorination using functionalized linear hydrocarbon substrates. Using methyl hexanoate as a test substrate,

reactions involving either sulfuryl chloride (**Table 3-4**, entry 3) or Mn(TPP)Cl/NaOCl (entry 4) proceeded with relatively poor selectivity between the most electron-rich γ and δ positions. As observed with methylcyclohexane in **Table 3-2**, reactions with N-chloroamide 1 without added inorganic base resulted in a poorly selective reaction. Under our optimized conditions in the presence of base, we significantly increase the selectivity for the most electron-rich (δ) site in the molecule. Chlorination at the δ site accounts for 57.6% of all chlorination products (**Table 3-4**, entry 4) in excellent chemical yield (83% combined yield).

Table 3-4. Chlorination of methylhexanoate under various conditions

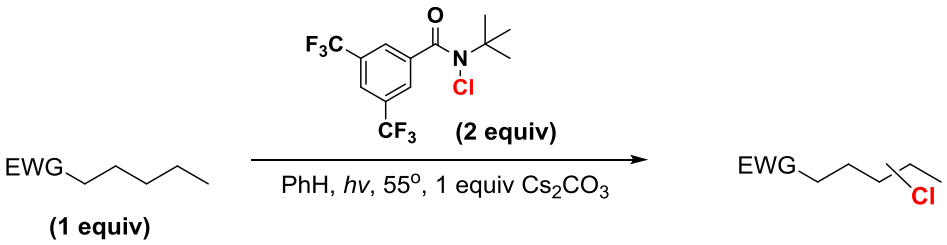


		chloroalkane isomer distribution (%) α β γ δ ω					
entry	conditions	MeO_2C—CH_2—CH_2—CH_2—CH_2—CH_3					
1	chloroamide **1 (2 equiv),** PhH, *hv,* 1 equiv Cs_2CO_3, 55°C	3.6	4.6	19.7	57.6	14.4	**(83% yield)**
2	chloroamide **1 (2 equiv),** PhH, *hv,* RT	---	10.8	37.9	42.4	8.9	
3	SO_2Cl_2, BPO, PhH, 85°C	---	12.1	37.7	42.0	8.2	
4	Mn(TPP)Cl, NaOBr	---	8.2	43.7	44.8	3.3	

We then surveyed a variety of synthetically versatile, electron-withdrawing functionality to determine the functional group tolerance of the reaction. The reaction was amenable to protected amines, nitriles, alkyl chlorides, acetates, and sulfonate groups (**Table 3-5**, entries 1−6). The δ selectivity in these studies ranged from 56% to 81%, with the phthalimide group providing the highest level of site selectivity. The general trend in these studies is greater δ selectivity with increased electron withdrawal of the substituent present on the alkyl chain. The chlorination of *n*-hexane indicates the possibility of a steric component to the C−H chlorination, with 65.5% 2-

chlorohexane produced. The preference for the most electron rich site in the molecule is greater than any existing C-H chlorination method.

Table 3-5. Electronically selective chlorination of diverse substrates[a]



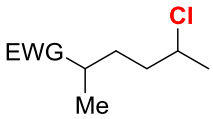
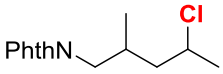
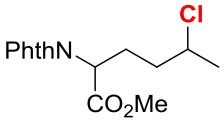
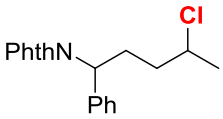
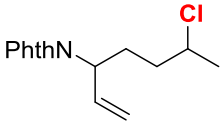
entry	substrate	% selectivity of bromination α (EWG—CH_2)	β (CH_2)	γ (CH_2)	δ (CH_2)	ω (CH_3)	combined yield (%)
1	PhthN	—	—	4.9	81.2	13.9	**80**
2	NC	—	—	15.0	65.9	19.1	**79**
3	Cl	9.2	5.7	15.3	56.9	12.9	**74**
4	AcO	—	9.0	19.8	57.3	13.8	**89**
5	Ph, S, O, O, O	3.5	5.9	16.2	56.2	18.1	**86**
6	Me	—	—	23.9	65.5	7.5	**70**

[a]Reactions were performed in PhH at 55° under Ar using visible light irradiation with 1 equiv of substrate and 2 equiv N-chloroamide. Yields were determined by GC analysis.

We further explored the site selectivity of the C−H chlorination with functionalized acyclic substrates containing more reactive tertiary, benzylic, and allylic C-H bonds. The results in (**Table 3-6**) clearly indicate that electronic (and possibly steric) factors are capable of deactivating these typically more reactive C−H bonds in favor of more electron-rich methylene sites. This electronically dictated selectivity is substantial with multiple functional groups, and with methyl substitution at both the α and β positions of the chain (**Table 3-6,** entries 1−4). The chlorination of phthalimide-protected norleucine methyl ester displays a major preference for the δ site (77.5%

selectivity) owing to the strong polar deactivation of the sites adjacent to the amino acid functionality. An area of significant interest was the possibility of achieving site-selective aliphatic C−H chlorination in the presence of substrate unsaturation. This chemoselectivity issue remains a roadblock in applying alkane functionalization to many complex substrates, particularly those containing alkenes. This is unsurprising given the propensity for electrophilic heterocycles or metal-oxo complexes, both widely used for alkane functionalization, to react with alkenes. Our preliminary studies in this area are promising (**Table 3-6**, entries 5 and 6), demonstrating successful C−H chlorinations of substrates with both arene and alkene substitution. In the case of the unsaturated substrate in entry 6 (**Table 3-6**) the majority of the chlorination occurs at a C-H bond that is roughly 20 kcal/mol that the tertiary allylic site in the molecule.

Table 3-6. Site Selectivity in the Presence of Activated C–H Bonds and Substrate Unsaturation

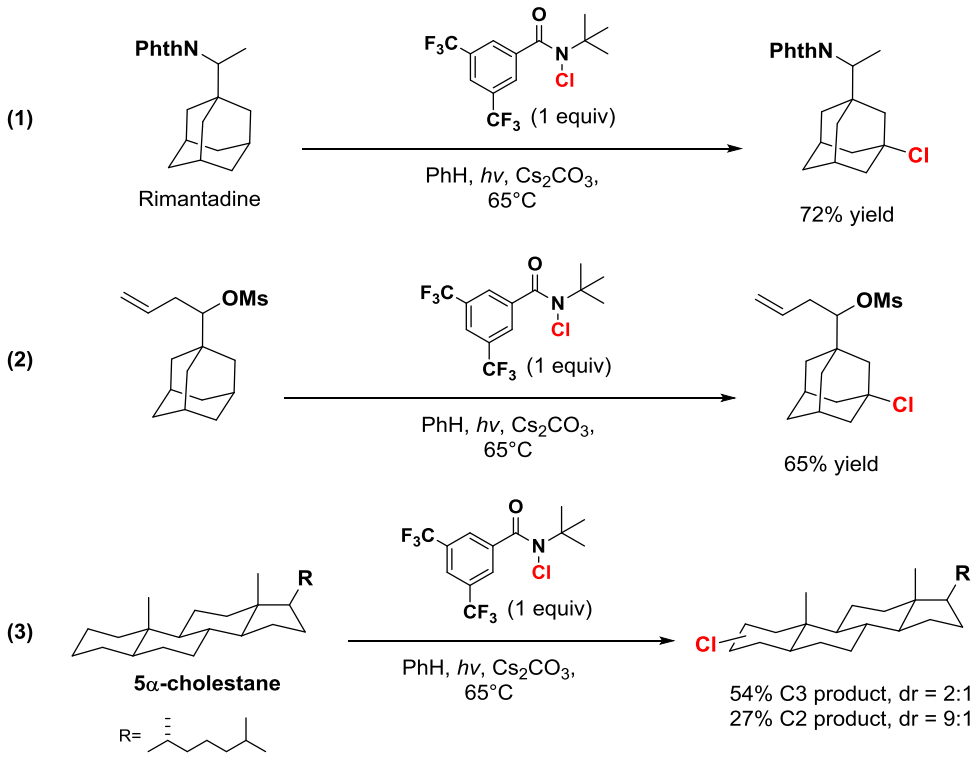
entry	major chlorination product	%selectivity	combined yield (%)	sites of minor chlorination (% selectivity)
				
1	EWG=PhthN	75.4	88	γ= 8.8; ω= 15.7
2	EWG=$PhSO_3$	68.3	76	γ= 18.3; ω = 13.6
3		63.6	69	β= 2.4; γ = 7.5; ω = 26.5
4		77.5	66	ω= 22.5
5		67.9	81	γ= 14.9; ω= 17.1
6		74.0	78	α= 6.5; ω = 18.9

[a]Reactions were performed in PhH at 55° under Ar using visible light irradiation with 1 equiv of substrate and 2 equiv N-chloroamide. Yields were determined by GC analysis.

3.3.4 Substrate Scope – Complex Molecules

Next we set out to apply our chlorination method to more complex substrates to determine the selectivity of the reaction in substrates that possess a combination of steric and electronic factors. We anticipate that this unique aspect of aliphatic C−H functionalization with tuned amidyl radicals will facilitate applications across a broad range of complex substrates. The ease of preparation of N-chloroamides, in addition to the useful levels of site selectivity in the reactions, offers attractive opportunities in the C−H chlorination of complex molecules (**Figure 3-1**). Functionalized adamantanes form the structural core of diverse small molecule drugs, yet there are few mild, site-selective protocols available for the C−H functionalization of these compounds. The

Figure 3-1. Aliphatic chlorination of drug-like molecules



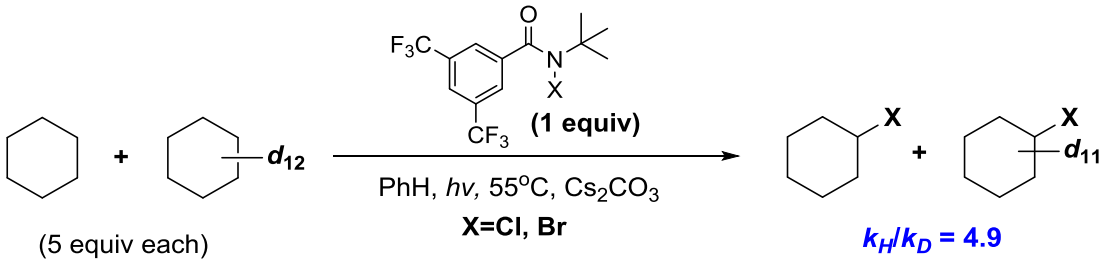
chlorination of the N-phthalimide derivative of antiviral drug rimantadine (**Figure 3-1,** entry 1) using N-chloroamide 1 provided a single chlorinated in good isolated yield (66%), with complete site selectivity for the less-hindered tertiary C−H site. We were particularly pleased that we were able to observe adamantane functionalization in the presence of a simple allyl group (**Figure 3-1**, entry 2). 5α-Cholestane is a challenging substrate for site-selective C−H functionalization owing to the presence of 48 unactivated C−H bonds with little electronic differentiation considering the absence of heteroatomic functionality. The functionalization of 5α-Cholestane using 1 equiv of reagent 1 favors C3-chlorination (C3:C2 =2:1) and provides an 81% yield of chlorinated products (eq 2). By comparison, the functionalization facilitated by the bulky, designed catalyst Mn(TMP)Cl (TMP = tetramesitylporphyrin) provides a C3:C2 of 1.5:1 in 55% yield using 3 equiv of NaOCl. While single-site selectivity is ultimately the goal of this chemistry the reaction 5α-Cholestane offers a potential benefit for the medicinal chemist whose seeks multiple derivatives for the purpose of developing a structure-activity-relationship (SAR).

3.3.5 Mechanistic Studies and Proposed Mechanism

To gain insight into the mechanism of the reaction we conducted competitive kinetic isoptope experiments similar to those used to probe the mechanism for the *N*-bromination reaction developed earlier (see **Chapter 2.3.5**). After arriving at our optimized conditions for the C−H chlorination, we determined the deuterium kinetic isotope effect by the competition reaction between cyclohexane and d_{12}-cyclohexane using *N*-chloroamide reagent 1. The observed primary kinetic isotope effect was $k_H/k_D = 4.9$ under these conditions, which is consistent with irreversible hydrogen atom abstraction. This is similar in magnitude, but not an identical value to the primary KIE of $k_H/k_D = 5.9$ reported for the aliphatic bromination reaction in **Chapter 2**. For the sake of a better comparison, the bromination of cyclohexane under these conditions (base, 55^{o}C) with the

N-bromo derivative of 1 also resulted in a k_H/k_D = 4.9, consistent with the same amidyl radical species participating in both C−H abstractions. Additionally, the high degree of similarity between the selectivity in the C-H chlorination and bromination reactions support the presence of the same active species. For a complete mechanistic proposal see **Chapter 2.3.5.**

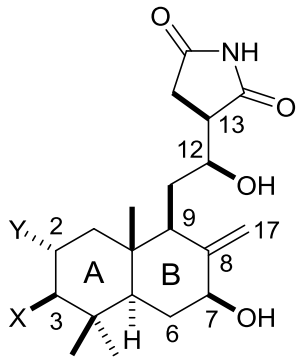
Figure 3-2. Competitive kinetic isotope experiment



3.4 Synthesis of *(+)-Chlorolissoclimide*

In the early 1990s, the groups of Malochet-Grivois and Roussakis described the structures and cytotoxic activities of the succinimide-containing labdane diterpenoids chlorolissoclimide and dichlorolissoclimide (**Figure 3-3**).[12,13] Initially, dichlorolissoclimide was shown to have potent activity against both the P388 murine leukemia cell line (IC50 = 2.4 nM) and the KB human oral carcinoma cell line (33 nM).[12a] Later, both chlorolissoclimide and dichlorolissoclimide were shown to interfere with the cell cycle at the G1 phase of nonsmall-cell bronchopulmonary carcinoma cells (NSCLC-N6), causing antiproliferation.[15b]

Figure 3-3. Activities (IC50 values) of chlorolissoclimide, dichlorolissoclimide and haterumaimide Q against cancer cell lines



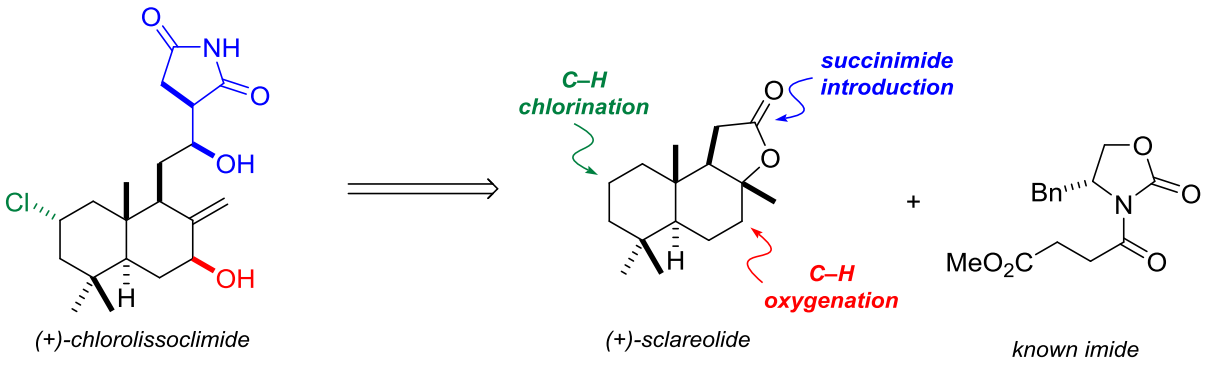
chlorolissoclimide (X = H, Y = Cl):
P388: 4.4 nM
KB: 0.14 mM
NSCLC: 26 nM

dichlorolissoclimide (X = Y = Cl):
P388: 2.4 nM
KB: 33 nM
NSCLC: 22 nM

haterumaimide Q (X = Y = H):
P388: 0.14 mM

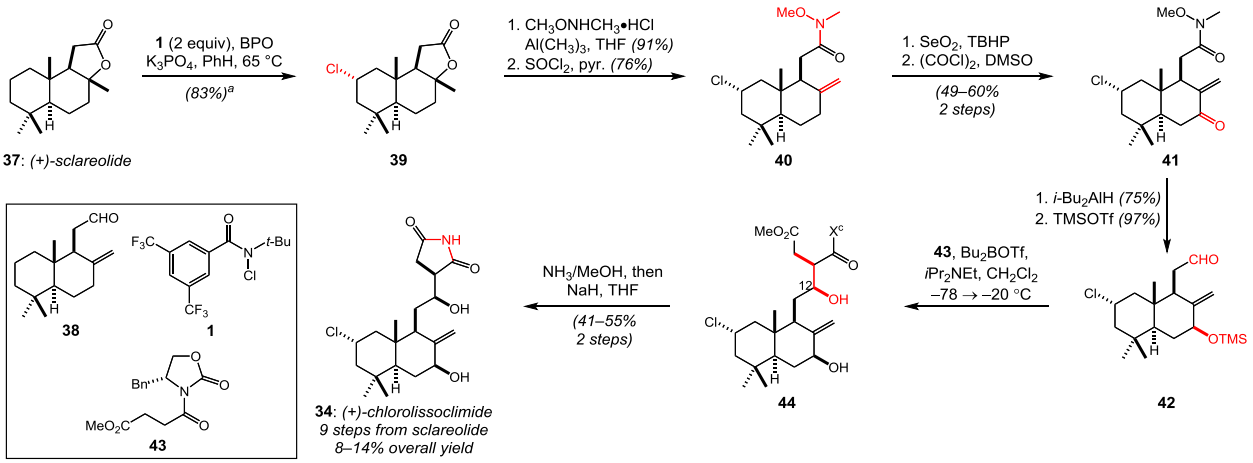
Since 2001, the groups of Ueda/Uemura and Schmitz have reported about 20 closely related labdane diterpenoids that they have called the haterumaimides (**Figure 3-3**).[14] Many of these compounds show equally impressive levels of cytotoxicity. In spite of the obvious potential interest in these compounds from the biological perspective, as well as some particularly interesting biogenetic peculiarities, both the C2- chloride and the succinimide are very unusual. Only three groups have reported work toward these compounds: (1) Jung and co-workers studied methods to introduce the two chlorides relevant to dichlorolissoclimide onto simplified decalin scaffolds.[15] (2) The González/Betancur-Galvis and (3) Chai groups looked at methods to install the succinimide group onto aldehyde 38 (**Figure 3-5**) derived from readily available (+)-sclareolide (37); the former study used an unselective aldol addition of a succinimide enolate,[16] and the latter used Evans aldol chemistry tointroduce the heterocycle via a four-step sequence, but could not avoid isomerization of the C8−C17 exocyclic alkene into the endocyclic positions, nor could these isomers be fully separated from one another.[17] In short, there have been no completed syntheses in this family of structurally and biologically intriguing natural products.

Figure 3-4. Retrosynthetic analysis for the synthesis of chlorolissoclimide



As part of a broader study of this family of diterpenoids, we questioned whether C−H functionalization methods might permit the conversion of sclareolide to chlorolissoclimide (**Figure 3-4**). In reverse order, key steps would include the stereocontrolled introduction of the β-hydroxysuccinimide, which had proved challenging in earlier studies, stereoselective C7-oxygenation, and regio- and stereoselective C2-chlorination.. Previous reports strongly suggested that the C2 position of sclareolide is the most activated for C−H functionalization under radical conditions.[18] Prompted by the efficient C2- bromination of sclareolide from the Alexanian group,[4] a collaboration was borne to gain efficient access to 2-chlorosclareolide for the purposes of a concise synthesis of chlorolissoclimide. Using reagent 1, we converted sclareolide into 2-chlorosclareolide with remarkable efficiency, even on gram scale. The selectivity of this reagent is outstanding: only product **39** and traces of residual sclareolide can be observed in the ^{1}H NMR spectra of the crude reaction product. Weinreb aminolysis of the lactone and dehydration of the tertiary carbinol, following a process previously performed on sclareolide,[19] afforded **40** in good yield. C7-oxygenation was performed by selenium dioxide mediated allylic oxidation[20] to afford the axial C7 allylic alcohol, which was subjected to Swern oxidation to give enone **41**. Concurrent reduction of the Weinreb amide and the enone was efficient and stereoselective for the introduction of the equatorial C7-hydroxyl group (**Figure 3-5**).

Figure 3-5. Forward synthesis of chlorolissoclimide

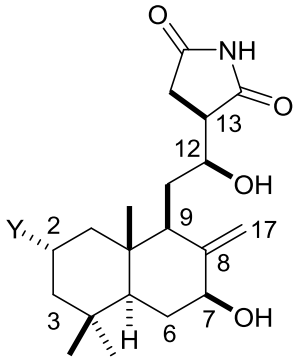


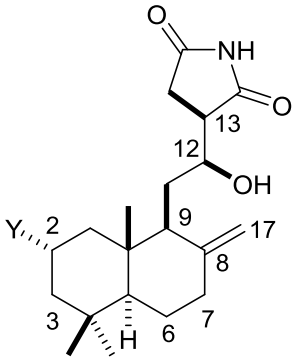
Silylation of this alcohol afforded **42**, whose aldehyde was subjected to our optimized sequence for introduction of the β- hydroxysuccinimide. Evans aldol addition of known imide **43**[21] to aldehyde **42** was initially low-yielding and inconsistent, which we attributed to nonproductive coordination of the boron Lewis acid to the pendant ester of **43**. This issue was resolved by pretreatment of **43** with dibutylboron triflate for 30 min at −78 °C prior to addition of Hünig's base, resulting in a reliable aldol addition. The labile TMS ether, which is important for reaction efficiency, is cleaved in this step. Direct ammonolysis of the crude imide in methanol prevented the undesired lactone formation previously observed by Chai and co-workers; immediate imide formation via the presumed *N*-sodiated amide directly affords the β-hydroxysuccinimide without alkene migration and completes the first synthesis of (+)-chlorolissoclimide. This sequence is general and reliable, and this technical advance will prove important in the synthesis of the whole family of lissoclimides/haterumaimides. Notably, chlorolissoclimide is obtained in up to 14% overall yield via the nine-steps equence described in **Figure 3-5**.

Variants of the same sequence have led to the synthesis of haterumaimide Q and the 7-deoxy analogues of both 34and 36 (**Figure 3-6**).[22] We have evaluated all four compounds for their

toxicity to aggressive prostate andmelanoma cancer cell lines (DU145 and A2058, respectively). While we have found these compounds to be active at about the micromolar level, they are clearly much less potent toward these more relevant cell lines compared with the P388 murine leukemia cell line, against which all haterumaimides and lissoclimides have previously been tested. Clearly a larger panel of cell lines should be evaluated, given the previously reported potency of chlorolissoclimide against nonsmall-cell lung cancer (IC50 = 26 nM; **Figure 3-3**). With respect to the two cell lines evaluated in this study, we recognize that this series of compounds affects both the prostate and melanoma cell lines about equally and that the activities vary less than an order of magnitude depending upon the presence or absence of a C2-chloride or a C7-hydroxyl group.

Figure 3-6. Activities of chlorolissoclimide and analogues against aggressive tumor cell lines





chlorolissoclimide (Y = Cl):
A2058: 0.30 μM
DU145: 0.56 μM

haterumaimide Q (Y = H):
A2058: 2.30 μM
DU145: 1.5 μM

7-deoxy*chlorolissoclimide* (Y = Cl):
A2058: 0.63 μM
DU145: 1.10 μM

7-deoxyhaterumaimide Q (Y = H):
A2058: 1.90 μM
DU145: 1.90 μM

3.5 Summary

In conclusion, we report a practical, site-selective approach to aliphatic C−H chlorination using N-chloroamides and visible light. While the chlorination of alkanes is commonly a poorly selective process owing to the promiscuity of the chlorine free radical, these amidyl radical-mediated reactions provide sterically and electronically dictated site selectivities that enable chlorination of complex molecules with diverse C−H bonds. These studies also indicate the potential for chemoselective aliphatic C−H functionalization in the presence of alkenes and arenes. The trivial preparation of N-chloroamides, and the use of substrate as the limiting reagent in all cases, bodes well for applications in complex synthesis. In that vein, we also report the first synthesis of natural products in the lissoclimide/haterumaimide family of potent cytotoxins using this chlorination method as the first step. Our semisynthesis of chlorolissoclimide starting with the gram-scale selective chlorination of (+)-sclareolide is short and efficient and includes the first example of a stereocontrolled C−H halogenation for the incorporation of a halogen-bearing stereogenic center of a natural product.[23] The transformation itself is likely relevant to the biosynthesis of the 2-chlorinated lissoclimides and haterumaimides. That this chlorination reaction can support the synthesis of a complex natural product clearly demonstrates its practicality. Additionally, in the context of the chlorolissoclimide synthesis, we have developed a straightforward and general solution to the β-hydroxysuccinimide motif that is common to all active members of this natural product family. Finally, we have learned that chlorolissoclimide (34) and analogues haterumaimide Q (36), 7-deoxychlorolissoclimide (45), and 7-deoxyhaterumaimide Q (46) are cytotoxic to aggressive melanoma and prostate cancer cell lines with IC50 values of about 1 μM.Efforts to further improve the site selectivity of the C−H chlorination and applications to other complex substrates are underway. We are also in the process

of expanding our work in the synthesis of haterumaimide natural products to better understand their structure−activity relationship. Each of these studies will be reported in due course.

3.6 Experimental Data

3.6.1 General Methods

All reactions were performed in oven-dried (120 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Reaction solvents including dichloromethane (CH_2Cl_2, Fisher, HPLC Grade), hexanes (Fisher, HPLC Grade), diethyl ether (Et_2O, Fisher, BHT stabilized, HPLC Grade), benzene (C_6H_6, Fisher, HPLC Grade), tetrahydrofuran (THF, Fisher, HPLC Grade), and toluene ($PhCH_3$, Fisher, HPLC Grade) were dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon.

Solvents for workup and chromatography were: acetone (Fisher, ACS grade), hexanes (Fisher or EMD, ACS Grade), EtOAc (EtOAc, Fisher, ACS Grade), dichloromethane (CH_2Cl_2, Fisher, ACS Grade), and methanol (MeOH, Fisher, ACS Grade). Column chromatography was performed using EMD Millipore 60 Å (0.040–0.063 mm) mesh silica gel (SiO_2). Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 TLC plates. Visualization was accomplished with UV (254 or 210 nm), and *p*-anisaldehyde, or ceric ammonium molybdate and heat as developing agents.

Chloroform-*d* ($CDCl_3$, D 99.8%, DLM-7) and methanol-d_4 (CD_3OD, D 99.8%, DLM-24) and dichloromethane-d_2 (CD_2Cl_2, D 99.9%, DLM-23) were purchased from Cambridge Isotope Laboratories. Citric acid (ACS grade, anhydrous, Fisher), K_2CO_3 (anhydrous, 99%, Alfa Aesar),

$NaHCO_3$ (ACS grade, Fisher), NaOH (ACS grade, Macron or Fisher), $Na_2S_2O_3$ (ACS grade, Fisher), *p*-anisaldehyde (99%, Acros Organics), trimethylaluminum ($Al(CH_3)_3$, Sure Pack™reagent grade, Sigma Aldrich), benzoyl peroxide (BPO, reagent grade, Sigma Aldrich), *tert*-butylhydroperoxide (TBHP, 5.5 M in decanes, Sigma Aldrich), di-*iso*-butylaluminum hydride (*i*Bu_2AlH, Sure Pack™reagent grade, Sigma Aldrich), ammonia (2.0 M in methanol, Acros Organics), selenium (IV) oxide (SeO_2, 99.8%, Acros Organics), dimthyl sulfoxide (DMSO, extra dry with molecular sieves, water <50 ppm, Acros Organics) were used without further purification.

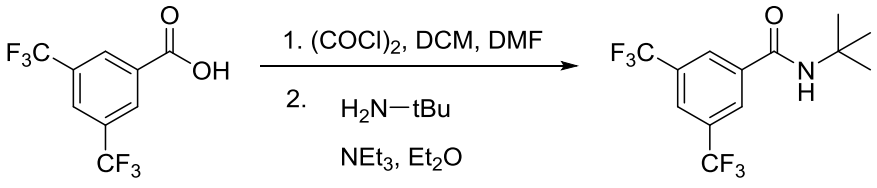
The following reagents were distilled from the indicated drying agents under argon prior to use: triethylamine (Et_3N, EMD, CaH_2), pyridine (Alfa Aesar, CaH_2), 2,4,6-collidine (Alfa Aesar, CaH_2), and *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt, Alfa Aesar, CaH_2). Oxalyl chloride ($(COCl)_2$, Sigma Aldrich) trimethylsilyl triflate (TMSOTf, Alfa Aesar), dibutylboron triflate (*n*Bu_2BOTf, Acros Organics), and thionyl chloride ($SOCl_2$, Sigma Aldrich), were fractionally distilled prior to use.

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. GC Spectra were obtained using a Shimadzu GC-2010 gas chromatograph with a Shimadzu AOC-20s Autosampler, and Shimadzu SHRXI-5MS GC column. The results of the kinetic isotope study were analyzed using an Agilent Gas Chromatograph- Mass Spectrometer with a 6850 series GC system and a 5973 Network Mass Selective Detector. Proton and carbon magnetic resonance spectra (^1H NMR and ^{13}C NMR) were recorded at 298K on a Bruker GN500 (500 MHz, ^1H; 125 MHz, ^{13}C), Bruker CRYO500 (500 MHz, ^1H; 125 MHz, ^{13}C), Bruker AVANCE600 (600 MHz, ^1H), Bruker model DRX 400, DRX 500, or a Bruker AVANCE III 600 CryoProbe (^1H NMR at 400, 500 or 600 MHz and ^{13}C NMR at 100, 126 or 151 MHz) spectrometer with solvent resonance as the internal standard (^1H NMR: $CDCl_3$ at 7.28 ppm, C_6D_6 at 7.16 ppm; ^{13}C NMR: $CDCl_3$ at

77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, tdd = triplet of doublet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. Mass spectra for the methods development were obtained using a Thermo LTqFT mass spectrometer with electrospray introduction and external calibration. Mass spectrometry data for the synthesis were obtained from the University of California, Irvine Mass Spectrometry Facility. High-resolution mass spectra (HRMS) were recorded on a Waters LCT Premier spectrometer using ESI-TOF (electrospray ionization-time of flight) and data are reported in the form of (*m/z*). Melting points (mp) were recorded on a Laboratory Devices Mel-Temp II melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on SiliaPlate 250μm thick silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 μm) purchased from Silicycle.

3.6.2 Compound Preparation

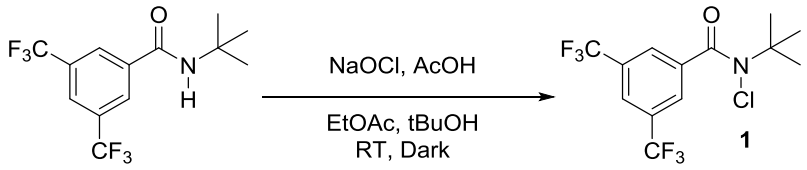
Amide Synthesis



***N*-(tert-butyl)-3,5-bis(trifluoromethyl)benzamide** was synthesized by reacting tert-butylamine with the corresponding acid chloride in THF. To a 0 ºC solution of 10.0g carboxylic acid (38.75 mmol) in DCM (150 mL) and DMF (100 uL) was added 6.5 mL oxalyl chloride (71.50 mmol)

dropwise under an argon atmosphere. The solution was stirred at 0 ºC for 15 min. then warmed to room temperature for 1.5 hours. The resultant solution was evaporated almost to dryness under reduced pressure to remove the DCM. The reaction mixture was dissolved in dry THF and cooled to 0 °C. Then 10.1 mL of tertbutylamine (71.5 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight. The reaction was diluted with Et_2O, washed with a 2.5M NaOH solution, 3x 1M HCl solution, 1x Brine, dried with magnesium sulfate and concentrated under reduced pressure. The product was purified via single solvent recrystallization from benzene to give the product (11.1 g, 35.5 mmol, 92% yield) as a white crystalline solid. Physical and spectral data were in accordance with literature data.[24]

N-Chlorination with Sodium Hypochlorite



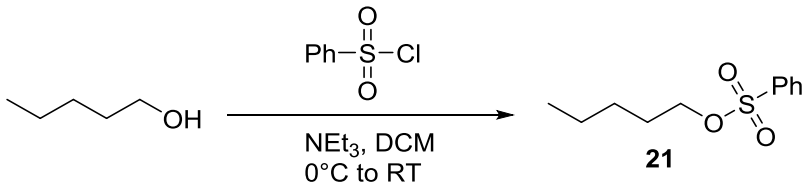
General Procedure: To a 250 mL foil wrapped flask under N_2, amide (3.50 g, 11.2 mmol) was added and dissolved in a mixture of ethyl acetate (20 mL) and *tert*-butanol (0.85 mL, 11.2 mmol). 50 mL of a sodium hypochlorite solution was then added (~1.5M in H_2O Sigma-Aldrich), followed by acetic acid (6.4 mL, 112 mmol). The reaction was stirred at room temperature for 3-4 hours. When the reaction was complete as judged by TLC analysis (3 hours usually sufficient) the reaction was diluted with Et_2O, washed three times with saturated sodium bicarbonate solution, once with water, and once with brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The crude material usually contains traces of chlorinated ethyl acetate. The crude product was purified via column chromatography (1-5% EtOAc/Hexane) to give the choloroamide product (3.8g, 10.9 mmol, 98% yield) as a clear oil. *General storage: N-*

Chloro reagents were stored in foil-wrapped vials in the freezer when not in use. The reagents can be weighed out on the bench top without risk of decomposition.

Analytical data for **Chloroamide** : **^{1}H NMR** ^{1}H NMR (600MHz ,CHLOROFORM-d) δ = 8.09 (s, 2 H), 7.97 (s, 1 H), 1.62 (s, 9 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 125 MHz) 172.2, 138.3, 131.9, 131.7, 131.5, 131.3, 128.6, 125.6, 124.4, 124.3, 124.2, 124.1, 123.8, 122.0, 120.2, 64.7, 27.9 ppm; **IR** (thin film, cm^{-1}) 2985.3, 2939.9, 1459.9, 1385.6, 1369.2, 1182.2, 1139.7, 906.4, 702.9, 681.7; **HRMS** (ESI) Calcd. for $[C_{13}H_{12}NClF_6O_3+Na]^+$ = 370.04, Found = 370.04.

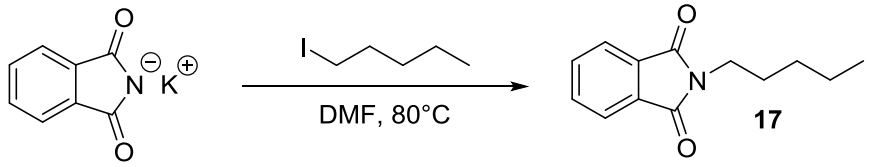
Substrate Synthesis

Note: Hydrocarbon substrates were obtained commercially and used without further purification unless otherwise noted.



Benzenesulfonyl Pentanol (21). To a 0° solution of pentanol (2.46 mL, 22.7 mmol) and trimethylamine (4.16 mL, 29.49 mmol) in DCM (25 mL) benzenesulfonyl chloride was added dropwise. The reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with Et_2O (100 mL) and the organic layer was washed twice with 100 mL of 1N HCL solution, and once with brine. The organic layer was then dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified using column chromatography (5-10% EtOAc/Hexanes) to isolate benzenesulfonyl pentanol (4.77 g, 20.9 mmol, 92% yield) as a clear liquid.

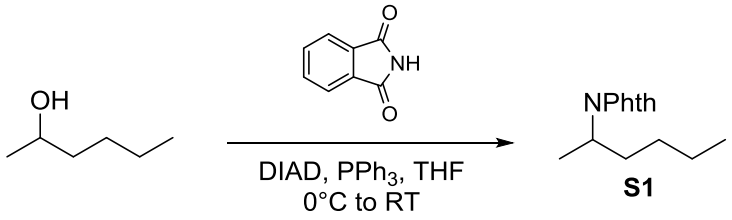
Analytical data for **Benzensulfonyl Pentanol:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.92 (d, *J* = 8.3 Hz, 2 H), 7.67 (s, 1 H), 7.61 - 7.53 (m, 2 H), 4.05 (t, *J* = 6.6 Hz, 2 H), 1.69 - 1.59 (m, 2 H), 1.33 - 1.20 (m, 4 H), 0.85 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 136.2, 133.7, 129.2, 127.8, 70.9, 28.5, 27.4, 22.0, 13.8 ppm; **IR** (thin film, cm^{-1}) 2959.2, 2934.1, 2870.5, 1449.2, 1360.3,1186.9, 1097.3, 958.4, 914.1, 826.4, 755.9, 590.1; **HRMS** (ESI) Calcd. for $[C_{11}H_{16}SO_3+Na]^+$ = 251.07, Found = 251.07.



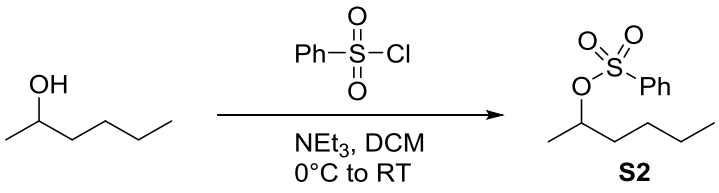
***N*-Pentyl Phthalimide (17):** was synthesized via an alkylation reaction of iodopentane with phthalimide potassium salt: To a room temperature solution of iodopentane (2.5 mL, 19.14 mmol) in DMF (200 mL), the phthalimide salt (7.09 g, 38.3 mmol) was added. The reaction was headed to 80 °C overnight. The reaction was cooled to room temperature and diluted with Et_2O and water. The organic layer was separated and washed 8 times with 100 mL of water to remove the residual phthalimide salt. The organic layer was then dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified using column chromatography (25% EtOAc/Hexanes) to isolate N-Phth pentane (3.45 g, 15.5 mmol, 82% yield) as a clear, yellowish liquid.

Analytical data for ***N*-Pentyl Phthalimide:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.88 - 7.75 (m, 1 H), 7.73 - 7.59 (m, 2 H), 3.74 - 3.56 (m, 2 H), 1.75 - 1.57 (m, 2 H), 1.31 (br. s., 4 H), 0.94 - 0.79 (m, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.4, 133.8, 132.1, 123.1,

37.9, 28.9, 28.2, 13.9 ppm; **IR** (thin film, cm^{-1}) 3468.4, 3061.4, 2934.2, 1773.2, 1712.5, 1614.13, 1465.6, 1397.2, 1367.3, 1186.0, 1058.7, 980.6880.3, 793.5, 719.3, 620.0, 530.3; **HRMS** (ESI) Calcd. for $[C_{13}H_{15}NO_2+H]^+$ = 218.11, Found = 218.04.

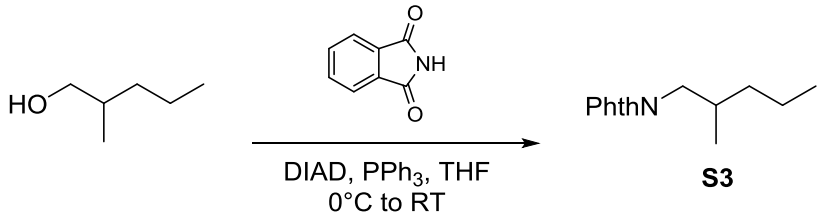


2-Phthalimidyl Hexane (S1). Phthalimide substrate **S1** was prepared via Mitsunobu reaction from the corresponding alcohol. To a 250 mL flame-dried round bottom flask 2-hexanol (1.2 mL, 9.8 mmol) was added and dissolved in THF. Phthalimide (2.16 g, 14.7 mmol) and triphenylphosphine (3.85 g, 14.7 mmol) were then added and the reaction was cooled to 0°C. Diisopropyl azodicarboxylate (2.97 mL, 14.7 mmol) was then added dropwise over 5 min. The reaction was allowed to warm to room temperature and stir overnight. When the reaction was complete by TLC the reaction was concentrated under reduced pressure and purified directly via column chromatography (20% EtOAc/Hexane) to give the product (1.7 g, 7.2 mmol, 73% yield) as clear oil. Physical and spectral data were in accordance with literature data.[25]



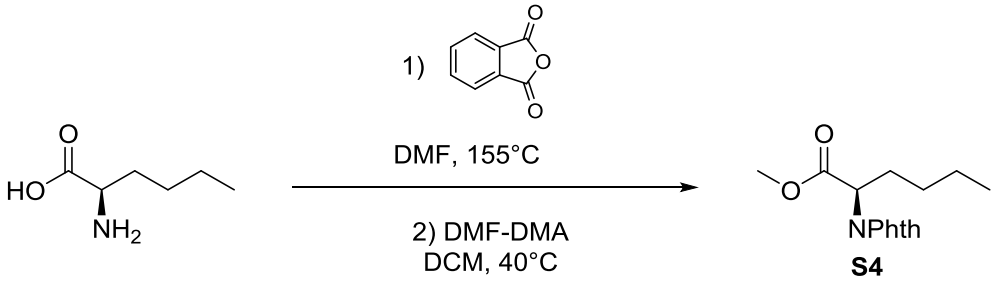
S2. Sulfonate substrate **S2** was prepared via a condensation reaction from the corresponding alcohol in an identical manner as described above for **benzenesulfonyl pentanol.** The crude material was purified using column chromatography (5-10% EtOAc/Hexanes) to isolate **S2** (1.5 g,

6.1 mmol, 94% yield) as a clear yellowish liquid. Physical and spectral data were in accordance with literature data.[26]



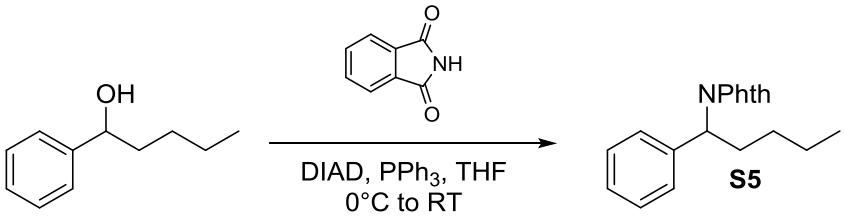
S3. Phthalimide substrate **S3** was prepared via Mitsunobu reaction from the corresponding alcohol in an identical manner as described above for substrate **S3**. The crude reaction mixture was purified directly via column chromatography (20% EtOAc/Hexane) to give the product (1.6 g, 6.9 mmol, 70% yield) as clear oil.

Analytical data for **S3:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.92 - 7.82 (m, 2 H), 7.77 - 7.70 (m, 2 H), 3.64 - 3.45 (m, 2 H), 2.07 - 1.95 (m, 1 H), 1.51 - 1.40 (m, 1 H), 1.40 - 1.26 (m, 2 H), 1.23 - 1.09 (m, 1 H), 0.95 - 0.86 (m, 6 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.7, 133.8, 132.1, 123.2, 44.4, 36.6, 32.4, 19.9, 17.4, 14.3 ppm; **IR** (thin film, cm^{-1}) 2959.2, 2930.3, 1773.3, 1711.5, 1465.6, 1435.7, 1398.1, 1186.97, 1061.6, 723.2; **HRMS** (ESI) Calcd. for $[C_{14}H_{17}NO_2+Na]^+$ = 254.12, Found = 254.12.



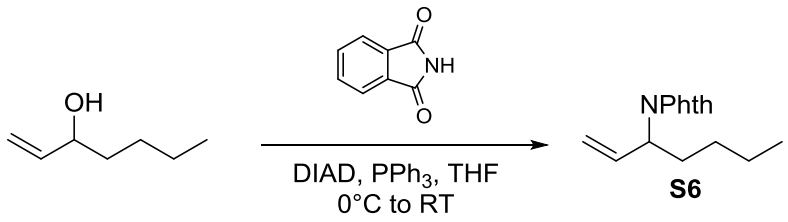
S4 was synthesized via the following two step protocol. To a flame-dried 25 mL flask 1.0 g (7.6 mmol) of DL-norleucene was added, followed by phthalic anhydride (1.7 g, 11.4 mmol). The two

solids were then dissolved in DMF (15 mL) and heated to 155° C for 12 hours. The reaction was cooled to room temperature and poured into 50 mL of 1N HCl, and cooled to 0° C for 20 minutes (if precipitation does not occur extract with Et_2O to isolate). The phthalimide product precipitates as a colorless solid which was collected (2. g 7.6 mmol, *quant*) via vacuum filtration and dried under vacuum. The phthalimide was used in the next step without further purification. Phthalimide protected norleucene (2.0 g, 7.6 mmol) was added to a flask fitted with a reflux condenser and dissolved in DCM (25 mL). Dimethylformamide-dimethylacetal (3.1 mL, 22.9 mmol) was then added dropwise and the reaction was refluxed for 4h. When TLC analysis revealed the reaction was complete, the reaction was cooled to room temperature, diluted with Et_2O, washed twice with saturated sodium bicarbonate solution, four times with saturated ammonium chloride solution, and once with brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified via colum chromatography (30-40% EtOAc/Hexanes gradient) to give **S4** (1.98 g, 7.2 mmol, 96% yield) as a yellowish oil. Physical and spectral data were in accordance with literature data.[27]



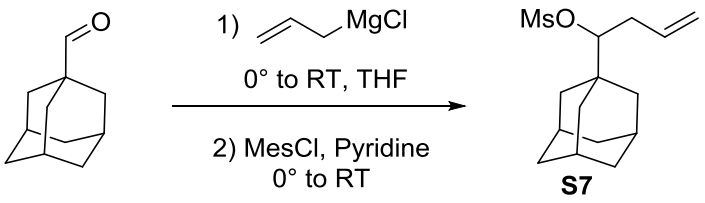
S5. Phthalimide substrate **S5** was prepared via Mitsunobu reaction from the corresponding alcohol in an identical manner as described above for substrate **S1**. The crude reaction mixture was purified directly via column chromatography (25% EtOAc/Hexane) to give the product (2.1 g, 7.1 mmol, 74% yield) as clear oil.

Analytical data for **S5:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.84 - 7.80 (m, 2 H), 7.72 - 7.68 (m, 2 H), 7.58 (d, *J* = 7.7 Hz, 2 H), 7.35 (t, *J* = 7.7 Hz, 2 H), 7.28 (t, *J* = 1.0 Hz, 1 H), 5.47 - 5.21 (m, 1 H), 2.72 - 2.46 (m, 1 H), 2.36 - 2.25 (m, 1 H), 1.47 - 1.29 (m, 4 H), 0.91 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.4, 139.9, 133.9, 131.9, 128.5, 128.2, 127.8, 123.2, 55.1, 30.7, 29.2, 22.3, 14.0 ppm; **IR** (thin film, cm^{-1}) 3062.4, 3031,5, 2958.3, 2929.3, 2867.6, 1773.2, 1711.5, 1465.6, 1387.5, 1068.9, 880.3, 721.2; **HRMS** (ESI) Calcd. for $[C_{19}H_{19}NO_2+Na]^+$ = 316.13, Found = 316.13.



S6. Phthalimide substrate **S6** was prepared via Mitsunobu reaction from the corresponding alcohol in an identical manner as described above for substrate **S1**. The crude reaction mixture was purified directly via column chromatography (20% EtOAc/Hexane) to give the product (1.4 g, 5.7 mmol, 67% yield) as clear oil.

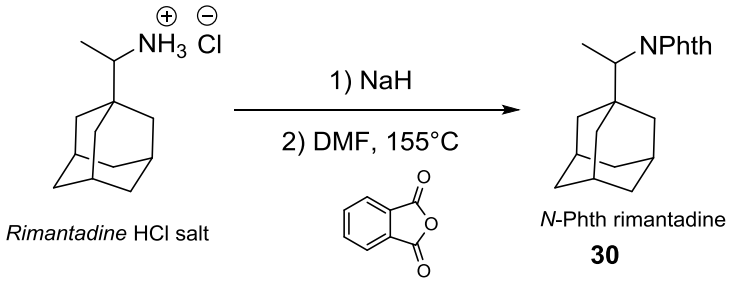
Analytical data for **S6:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) d = 7.87 - 7.78 (m, 2 H), 7.75 - 7.63 (m, 2 H), 5.71 (dddd, *J* = 5.9, 8.4, 10.1, 17.1 Hz, 1 H), 5.03 (d, *J* = 18.3 Hz, 0 H), 4.94 (d, *J* = 10.3 Hz, 1 H), 4.29 (tt, *J* = 5.2, 10.2 Hz, 1 H), 2.81 (td, *J* = 9.2, 14.2 Hz, 1 H), 2.55 - 2.46 (m, 1 H), 1.75 (tdd, *J* = 5.4, 10.3, 13.8 Hz, 1 H), 1.39 - 1.17 (m, 4 H), 0.86 (t, *J* = 7.3 Hz, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.1, 135.9, 133.9, 131.9 123.2, 117.3, 54.2, 31.7, 28.6, 22.2, 13.9 ppm; **IR** (thin film, cm^{-1}) 2961..2, 2931.2, 2874.4, 1465.6, 1450.2, 1360.5, 1186.1, 1097.3, 966.2, 820.6, 756.9, 689.4, 590.1; **HRMS** (ESI) Calcd. for $[C_{15}H_{17}NO_2+Na]^+$ = 266.12, Found = 266.10.



S7 was synthesized via the following two step protocol starting from 1-adamantanecarboxaldehyde (accessed via a protocol reported by Leadbeater).[28] To a 0° solution of aldehyde (3.92 g, 16.2 mmol) in THF (80 mL) allylmagnesiumchloride solution (21 mL, 1.0M in THF) was added dropwise. The reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched with saturated ammonium chloride solution and extracted three times with ether. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified via column chromatography (10% EtOAc/Hexane) to give the product (2.9 g, 14.1 mmol, 87% yield) as colorless solid. The adamantanol (500 mg, 2.4 mmol) was then dissolved in pyridine (8 mL) and cooled to 0° C. Mesyl chloride was then added dropwise and the reaction was allowed to warm to warm to room temperature and stirred for 6 hours. When the reaction was complete judging by TLC analysis the crude reaction mixture was diluted with Et_2O, and washed three times with 1N HCl and once with brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified via column chromatography (10% EtOAc/Hexane) to give the product (655 mg, 2.3 mmol, 96% yield).

Analytical data for **S7: ^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 5.95 - 5.85 (m, 1 H), 5.23 - 5.12 (m, 2 H), 4.40 (dd, *J* = 2.9, 9.2 Hz, 1 H), 3.03 (s, 3 H), 2.54 (tdd, *J* = 1.4, 5.3, 15.0 Hz, 1 H), 2.44 - 2.35 (m, 1 H), 2.04 (br. s., 3 H), 1.77 - 1.70 (m, 3 H), 1.70 - 1.63 (m, 6 H), 1.59 (dd, *J* = 1.5,

12.1 Hz, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 135.4, 118.2, 91.6, 39.3, 38.2, 36.8, 36.7, 33.9, 28.1 ppm; **IR** (thin film, cm^{-1})2906.2, 2851.2, 1642.1, 1451.2, 1333.5, 1171.5, 905.4, 791.4, 732.8, 539.0; **HRMS** (ESI) Calcd. for $[C_{15}H_{24}SO_3+Na]^+$ = 307.13, Found = 307.14.



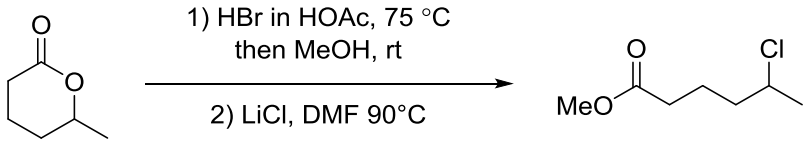
***N*-Phth Rimantadine (30).** The hydrochloride salt (1.44 g, 6.7 mmol) was dissolved in DMF (15 mL) and cooled to 0 °C. Neat sodium hydride (161.3 mg, 6.7 mmol) was then added with gas evolution and the reaction was stirred at 0 °C for 10 min. The reaction was then allowed to warm to room temperature over 30 min. Phthalic Anhydride (1.48 g, 10.4 mmol) was then added and the reaction was heated to reflux overnight. The reaction was then diluted with Et_2O and 1N HCl. The organic layer was separated and washed twice more with 1N HCl, and once with brine. The organic layer was then dried with magnesium sulfate and concentrated under reduced pressure. The crude material was purified using column chromatography (10% EtOAc/Hexanes) to isolate *N*-Phth Rimantadine (1.53 g, 4.95 mmol, 74% yield) as a white solid.

Analytical data for ***N*-Phth Rimantadine (30): ^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.93 - 7.79 (m, 2 H), 7.78 - 7.65 (m, 2 H), 4.05 (q, *J* = 7.3 Hz, 1 H), 1.99 (br. s., 3 H), 1.73 - 1.57 (m, 12 H), 1.51 (d, *J* = 7.3 Hz, 3 H); **^{13}C NMR** (125 MHz ,CHLOROFORM-d) δ = 169.5, 169.4, 133.9, 133.7, 132.3, 131.6, 123.2, 122.9, 56.8, 39.5, 37.8, 36.8, 28.4, 11.8 ppm, **IR** (thin film, cm^{-}

[1]) 2095.3, 2849.3, 2255.3, 1774.2, 1451.2, 1373, 1170.6, 1095.3, 912.2, 726.1, 531.3; **HRMS** (ESI) Calcd. for $[C_{20}H_{23}NO_2+H]^+$ = 332.16, Found = 332.16.

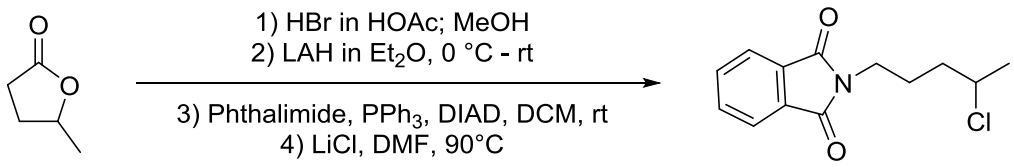
Synthesis of Chloride Standards

Note: Chloride standards were obtained commercially and used without further purification unless otherwise noted. Commercially obtained chloride include: chlorocyclohexane, 1-chloroadamantane, 2-chloroadamantane, 1-chlorohexane, 2-chlorohexane, 3-chlorohexane.

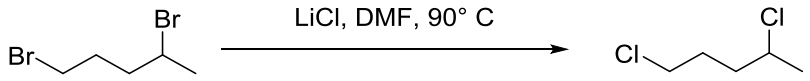


Methyl 5-chlorohexanoate was synthesized via the following two-step procedure: The first step of the procedure is adapted from the method reported by Wolf et. al.[29] The lactone (2.0 g, 17.5 mmol) was added to a flask containing a solution of 33% HBr in AcOH (5 mL) and fitted with a reflux condenser. The reaction was heated to 75 °C for 4 hours then cooled to room temperature, at which point methanol (8.0 mL) was added and the mixture was stirred at room temperature overnight. The reaction was then partially concentrated under reduced pressure, taken up in EtOAc, washed three times with a saturated aqueous solution of sodium bicarbonate, brine, and the organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified using column chromatography (5% EtOAc/Hexane) to isolate methyl 5-bromohexanoate 72% yield (2.05 g) as a clear liquid. Methyl 5-bromohexanoate (2.0 mL, 9.6 mmol) was then dissolved in DMF (15 mL) and lithium chloride was added in one portion (1.22 g, 28.9 mmol). The reaction was heated to 90° C and stirred overnight. When the reaction was

complete as judged my CG-MS analysis, the reaction was diluted with Et_2O, washed three times with 1N HCl, and once with brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The product required no purification. Physical and spectral data were in accordance with literature data.[30]

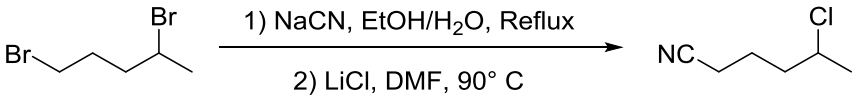


***N*-4-chloropentyl phthalimide** was synthesized via a four-step protocol. *N*-4-bromopentyl phthalimide was previously synthesized in our laboratory, for synthetic details regarding its synthesis see our previous publication. *N*-4-bromopentyl phthalimide (500 mg, 1.6 mmol) was then dissolved in DMF (5 mL) and lithium chloride was added in one portion (214 mg, 5.1 mmol). The reaction was heated to 90° C and stirred overnight. When the reaction was complete as judged my CG-MS analysis, the reaction was diluted with Et_2O, washed three times with 1N HCl, and once with brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified using column chromatography (15% EtOAc/Hexane) to isolate *N*-4-chloropentyl phthalimide (354 mg, 1.4 mmol, 88% yield) as a clear oil. Physical and spectral data were in accordance with literature data.[31]



1,4-Dichloropentane was prepared via substitution of the corresponding dibromide. 1,4-dibromopentane (1.0 g, 4.3 mmol) was dissolved in DMF (15 mL) and lithium chloride was added in one portion (1.1 g, 26.2 mmol). The reaction was heated to 90° C and stirred overnight. When the reaction was complete as judged my CG-MS analysis, the reaction was diluted with Et_2O, washed three times with 1N HCl, and once with brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified using column chromatography (2% EtOAc/Hexane) to isolate 1,4-Dichloropentane (467 mg, 3.3 mmol, 77% yield) as a yellowish liquid.

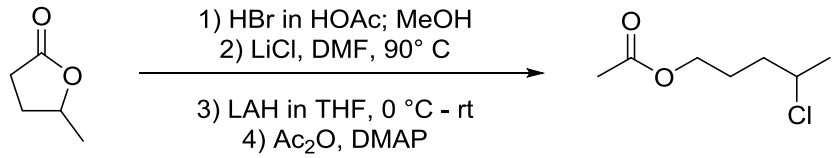
Analytical data for **1,4-Dichloropentane:** **^{1}H NMR** ^{1}H NMR (600MHz ,CHLOROFORM-d) δ = 4.12 - 4.01 (m, 1 H), 3.65 - 3.55 (m, 2 H), 2.11 - 2.00 (m, 1 H), 2.00 - 1.87 (m, 2 H), 1.87 - 1.77 (m, 1 H), 1.60 - 1.52 (m, 3 H); **^{13}C NMR** (125 MHz ,CHLOROFORM-d) δ = 57.9, 44.5, 37.4, 29.6, 25.5 ppm; **IR** (thin film, cm^{-1})2956.0, 2929.3, 1725.1, 1445.4, 1379.8, 1287.3, 773.3, 729.9, 652.8, 611.3; **LRMS** Calcd. for $[C_5H_{10}Cl_2]^+$ = 140.02, Found = 140.09



2-Chloro-5-Cyanopentane was prepared via a two-step protocol. 2-Bromo-5-Cyanopentane was previously synthesized in our laboratory, for synthetic details regarding its synthesis see our previous publication.[4] 2-Bromo-5-Cyanopentane (1.8 mL, 10.2 mmol) was then dissolved in DMF (15 mL) and lithium chloride was added in one portion (1.3 g, 30.6 mmol). The reaction was heated

to 90° C and stirred overnight. When the reaction was complete as judged my CG-MS analysis, the reaction was diluted with Et_2O, washed three times with 1N HCl, and once with brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified using column chromatography (10% EtOAc/Hexane) to isolate 2-Chloro-5-Cyanopentane (1.1 g, 8.6 mmol, 84% yield) as a yellowish liquid.

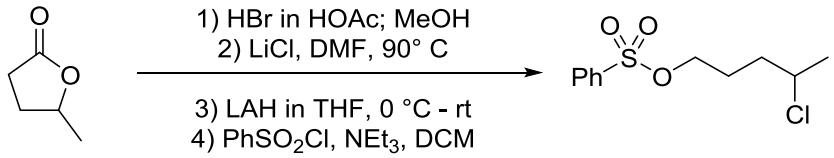
Analytical data for **2-Chloro-5-Cyanopentane: ^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 4.11 - 3.99 (m, 1 H), 2.47 - 2.37 (m, 2 H), 2.00 - 1.87 (m, 2 H), 1.86 - 1.75 (m, 2 H), 1.58 - 1.49 (m, 3 H); **^{13}C NMR** (125 MHz ,CHLOROFORM-d) δ = 119.3, 57.4, 38.8, 25.4, 22.6, 16.8 ppm; **IR** (thin film, cm^{-1}) 2972.2, 2932.3, 2874.4, 2246.6, 1454.1, 1429.9, 1379.8, 1255.4, 1123.3, 612.3; **HRMS** (ESI) Calcd. for $[C_6H_{10}ClN+Na]^+$ = 154.04, Found = 154.04**.**



4-Chloropentyl Acetate was synthesized via the following four-step protocol. The first step of the procedure is adapted from the method reported by Wolf et. al.[29] The lactone (2.0 g, 17.5 mmol) was added to a flask containing a solution of 33% HBr in AcOH (5 mL) and fitted with a reflux condenser. The reaction was heated to 75 °C for 4 hours then cooled to room temperature, at which point methanol (8.0 mL) was added and the mixture was stirred at room temperature overnight. The reaction was then partially concentrated under reduced pressure, taken up in EtOAc, washed three times with a saturated aqueous solution of sodium bicarbonate, brine, and the organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The crude product

(3.6 g, 17.5, *quant.*) was used in the next step without purification. The crude bromoester (2.0 g, 14.2 mmol) was dissolved in DMF (15 mL) and lithium chloride (1.8 g, 42.5 mmol) was added in one portion. The reaction was heated to 90° C and stirred overnight. When the reaction was complete as judged my CG-MS analysis, the reaction was diluted with Et_2O, washed three times with 1N HCl, and once with brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude chloroester (1.9 g, 13.1 mmol, 92% yield) was used in the next step without purification. The chloroester (2.0 g, 13.8 mmol) was added dropwise to a 0° solution of lithium aluminum hydride (675 mg, 20.7 mmol) in THF (30 mL). The reaction was stirred for 30 min at 0° then allowed to warm to room temperature and stirred for an additional 2 hours. The reaction was cooled back to 0° and quenched slowly by the sequential addition of water (2 mL), NaOH solution (4 mL, 2.5M), and water (10 mL). The reaction was filtered over celite, and concentrated under reduced pressure. The crude reaction mixture was diluted with Et_2O, washed with saturated sodium bicarbonate, and brine, dried with magnesium sulfate and concentrated under reduced pressure. The crude product was purified using column chromatography (15% EtOAc/Hexane) to isolate the chloro-alcohol (1.31g, 10.72 mmol, 78% yield) as a clear liquid. Lastly, the chloro-alcohol (500 mg, 4.1 mmol) was acetylated in in neat acetic anhydride (1 mL) using catalytic DMAP (24 mg, 0.2 mmol). The reaction was complete after stirring overnight at room temperature. The reaction was diluted with Et_2O, washed twice with saturated sodium bicarbonate, once with water, dried over magnesium sulfate and concentrated under reduced pressure. The product (660 mg, 4.0 mmol, 98% yield) did not require purification.

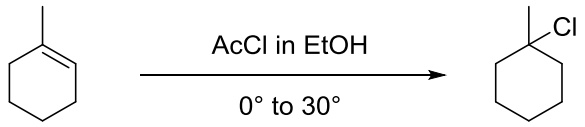
Analytical data for **4-Chloropentyl Acetate:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 4.15 - 4.01 (m, 3 H), 2.06 (s, 3 H), 1.94 - 1.70 (m, 4 H), 1.54 (d, *J* = 6.6 Hz, 3 H); **^{13}C NMR** (125 MHz, CHLOROFORM-d) δ = 171.1, 63.8, 58.2, 36.7, 25.9, 25.4, 20.9 ppm; **IR** (thin film, cm^{-1}) 2967.9, 1740.4, 1446.3, 1366.3, 1240.9, 1038.5, 608.4; **HRMS** (ESI) Calcd. for $[C_7H_{13}ClO_2+Na]^+$ = 187.04, Found = 187.04**.**



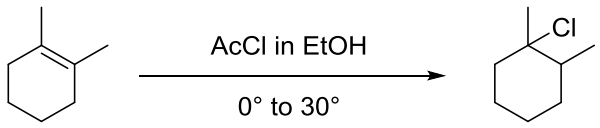
4-Chlorpentyl Benzenesulfonate was synthesized from the same chloroalcohol used to synthesize 4-Chloropentyl Acetate above. The chloroalcohol (500 mg, 4.1 mmol) was dissolved in DCM (8 mL) and triethyl amine (0.74 mL, 5.3 mmol) was added. The reaction was cooled to 0° and benzene sulfonyl chloride (0.57 mL, 4.5 mmol) was added dropwise. The reaction was allowed to warm to room temperature and was stirred overnight. When the reaction was complete as judged via TLC analysis the reaction was diluted with Et_2O, washed twice with 1N HCl and once with brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified using column chromatography (10% EtOAc/Hexane) to isolate 4-Chlorpentyl Benzenesulfonate (667 mg, 2.5 mmol, 62% yield).

Analytical data for **4-Chlorpentyl Benzenesulfonate:** **^{1}H NMR** ^{1}H NMR (600MHz ,CHLOROFORM-d) δ = 8.00 - 7.86 (m, 2 H), 7.74 - 7.64 (m, 8 H), 7.63 - 7.49 (m, 2 H), 4.16 - 4.04 (m, 2 H), 4.02 - 3.91 (m, 1 H), 1.97 - 1.86 (m, 1 H), 1.86 - 1.74 (m, 2 H), 1.74 - 1.63 (m, 1

H), 1.49 (d, *J* = 6.6 Hz, 3 H); **^{13}C NMR** (125 MHz ,CHLOROFORM-d) δ = 135.9, 133.9, 129.3, 127.9, 70.1, 57.8, 35.9, 26.1, 25.4 ppm; **IR** (thin film, cm^{-1}) 3067.2, 2972.7, 1447.3, 139.6, 1186.0, 1097.3, 969.3, 917.5, 826.7, 751.3, 689.4, 589.1; **HRMS** (ESI) Calcd. for $[C_{11}H_{15}ClSO_3+Na]^+$ = 385.03, Found = 385.03**.**



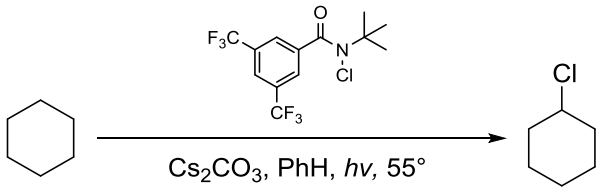
1-Chloro-1-Methylcyclohexane was synthesized according to literature procedures and used without purification. Physical and spectral data were in accordance with literature data.[32]



1-Chloro-1,2-Dimethylcyclohexane was synthesized according to literature procedures referenced above and used without purification. Physical and spectral data were in accordance with literature data. Both NMR and GC analysis show both the *trans* and *cis* products in a 87:13 ratio respectively. The selectivity is consistent with literature precedent.[33]

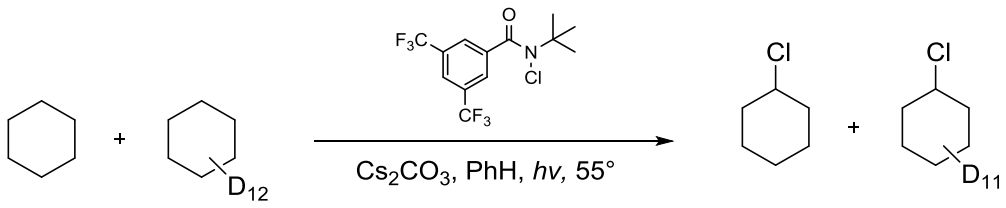
3.6.3 C-H Chlorination Procedures with N-Chloroamides

Chlorination of Cycloalkanes



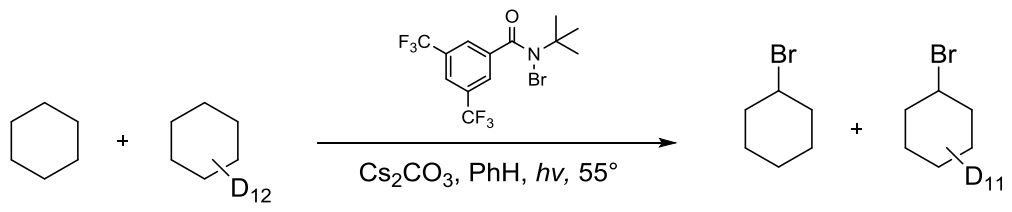
A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (50.0 mg, 0.143 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (280 μL). Cyclohexane (15.5 μL, 0.143 mmol), and cesium carbonate (46.2 mg, 0.143 mmol) were then added. *Note: cycloalkane was added as a stock solution in benzene to improve the reproducibility of the results.* The reaction was then sealed with teflon tape and taken out of the glovebox, and irradiated with two 23W compact fluorescent light bulbs for 90 minutes at 55° C. A white, semi-soluble precipitate forms as the reaction reaches completion. Upon competition, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 71.6% GC yield of cyclohexylchloride. A small amount of dichloride products (2% GC yield) are also formed in the reaction.

KIE Study



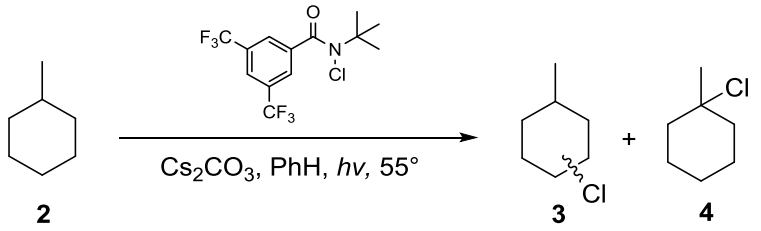
A flame-dried, 1 dram vial was charged with a stir bar and fitted with a PTFE lined screw cap. Chloroamide (20 mg, 0.058 mmol) was added to the vial in the absence of ambient light, and the

reaction was taken into a glovebox, and dissolved in 200 uL of dry, freeze-pump-thawed benzene. Cyclohexane (27.6 uL, 0.255 mmol) and Cyclohexane-d_{12} (27.5 uL, 0.255 mmol), and cesium carbonate (18.9 mg, 0.058 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 45 minutes at 55° C. The reaction was then diluted with DCM and analyzed using an Agilent Gas Chromatograph- Mass Spectrometer with a 6850 series GC system and a 5973 Network Mass Selective Detector to determine the ratio of non-deuterated to deuterated product (Ratio = 4.9 = $K_{H/D}$).



A flame-dried, 1 dram vial was charged with a stir bar and fitted with a PTFE lined screw cap. Bromoamide (20 mg, 0.058 mmol) was added to the vial in the absence of ambient light, and the reaction was taken into a glovebox, and dissolved in 200 uL of dry, freeze-pump-thawed benzene. Cyclohexane (27.6 uL, 0.255 mmol) and Cyclohexane-d_{12} (27.5 uL, 0.255 mmol), and cesium carbonate (18.9 mg, 0.058 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 45 minutes at 55° C. The reaction was then diluted with DCM and analyzed using an Agilent Gas Chromatograph- Mass Spectrometer with a 6850 series GC system and a 5973 Network Mass Selective Detector to determine the ratio of non-deuterated to deuterated product (Ratio = 4.9 = $K_{H/D}$).

Chlorination of Methylcyclohexane



Methylcyclohexane: A flame-dried, 1 dram vial was charged with a stir bar and. chloroamide (50.0 mg, 0.143 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (140 μL). Methylcyclohexane (18.2 μL, 0.143 mmol), and cesium carbonate (46.2 mg, 0.143 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 2 hours at 55° C. Upon competition, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The approximate yield was also verified with NMR analysis using 2,5 dimethylfuran as an internal standard. 74% GC yield of combined bromide products. *The secondary chloride products were assigned via analogy to our C-H bromination chemistry.*

Figure 3-7. Overlaid gas chromatogram for chlorination of methylcyclohexane with authentic 3^o product

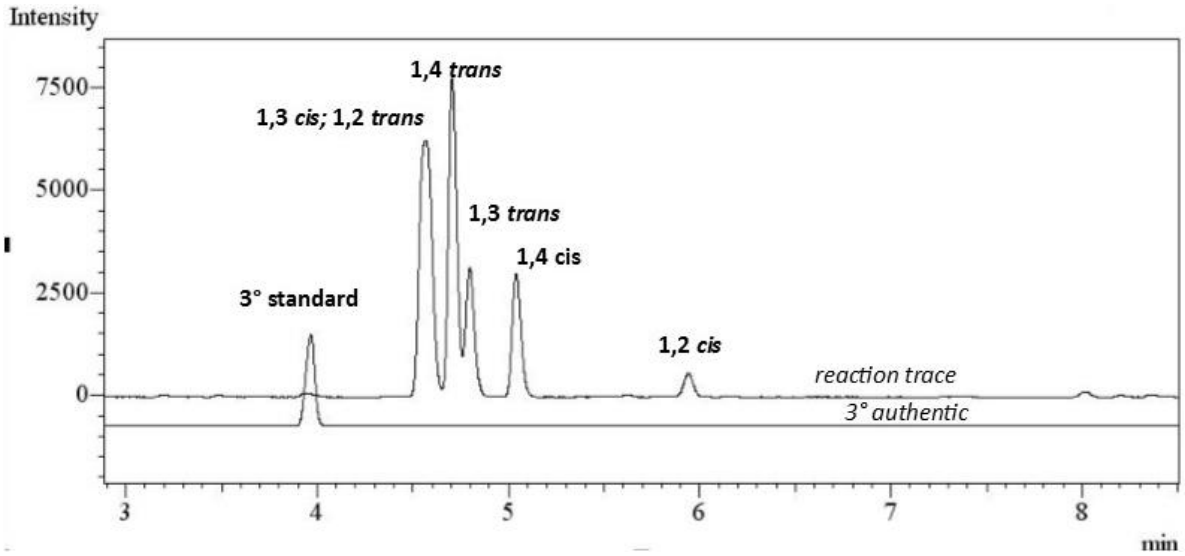
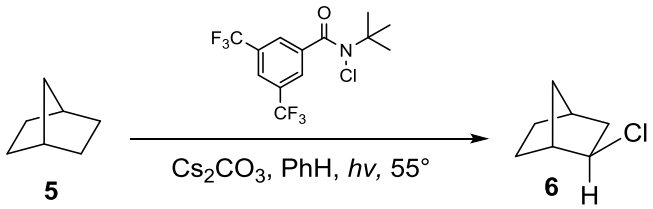


Table 3-7. Chlorination of methylcylohexane with chloroamide 1

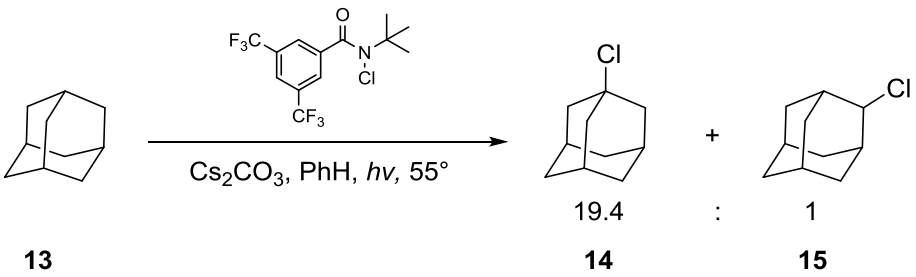
Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
3° chloride	4.00	1.51
1,3-*cis;* 1,2-*trans*	4.58	36.19
1,4-*trans*	4.75	31.58
1,3-*trans*	4.81	13.65
1,4-*cis*	5.05	14.65
1,2-*cis*	5.95	Trace

Bromination of Complex, Cyclic Alkanes



Norbornane: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (100.0 mg, 0.29 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (0.29 mL). Norbornane (27.9 mg, 0.29 mmol), and cesium carbonate (94.2 mg, 0.29

mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The reaction gives only the 2-exo product. 53.3% GC yield of 2-*exo*-chloronorbornane. The crude reaction mixture was purified using column chromatography (5% EtOAc/Hexane) to isolate 2-*exo*-chloronorbornane (18.2 mg, 0.14 mmol, 54% yield) as an off-white solid. Physical and spectral data were in accordance with literature data.[34]



Adamantane: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (50.0 mg, 0.143 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (140 μL). Adamantane (19.5 mg, 0.143 mmol), and cesium carbonate (46.7 mg, 0.143 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 2 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The reaction gives both 1-and 2-Chloroadamante in a 19 to 1 ratio by GC respectively. 69.3% GC yield of combined chloroadamantanes.

Figure 3-8. Overlaid gas chromatogram for chlorination of adamantane with authentic products

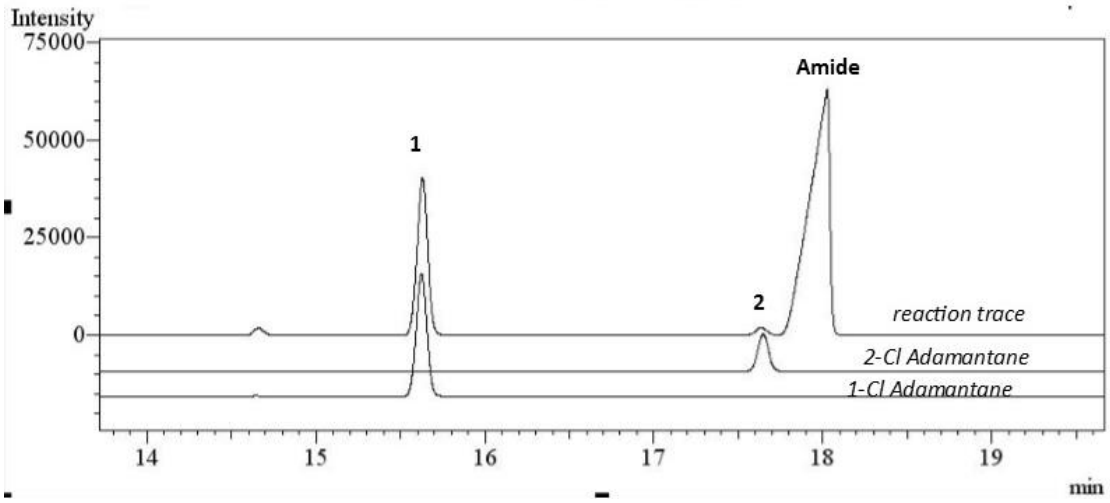
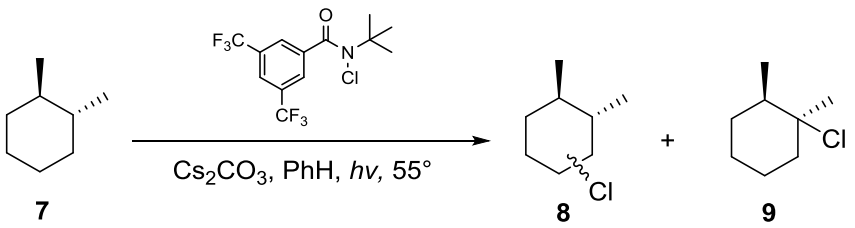


Table 3-8. Chlorination of adamantane with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
1-Chloroadamantane	15.63	94.91
2-Chloroadamantane	17.65	5.09



1,2-*trans*-dimethylcyclohexane: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide **1** (50.0 mg, 0.143 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (140 μL). 1,2-*trans*-dimethylcyclohexane (30.5 μL, 0.143 mmol), and cesium carbonate (46.7 mg, 0.058 mmol) were then added. The reaction was then

sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 2 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. Upon completion, the reaction mixture was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was run through a plug of silica and concentrated a second time. The reaction was analyzed by NMR using 2,5-dimethylfuran as an internal standard to determine the yield of secondary chloride products. GC analysis was used to determine the relative amount and yield, of the tertiary chloride products. 79.0% NMR yield of combined chloride products. *By analogy to our bromination chemistry, none of the cis tertiary product is observed in the reaction trace. Bromination of the trans isomer of starting material gives only 0.9% functionalization at a tertiary position to give only the trans isomer. Additionally, formation of the cis product from the trans isomer of starting material involves a thermodynamically unfavorable trapping step.*

Figure 3-9. Overlaid chromatogram for chlorination of 1,2 *trans* dimethylcyclohexane with authentic 3^{o} products

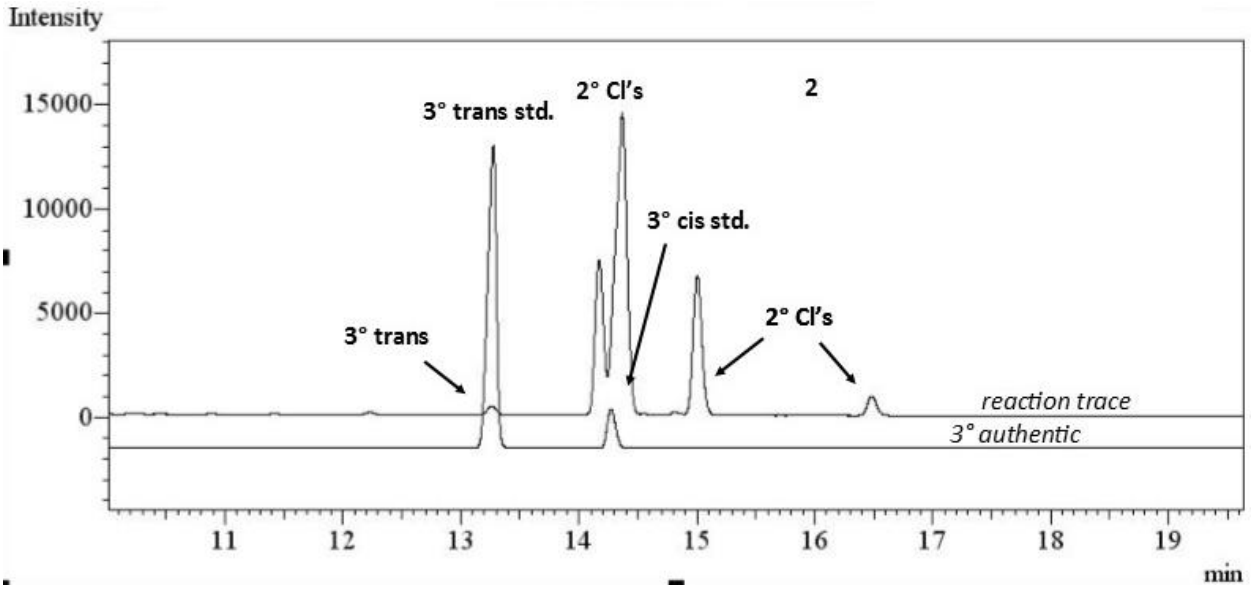
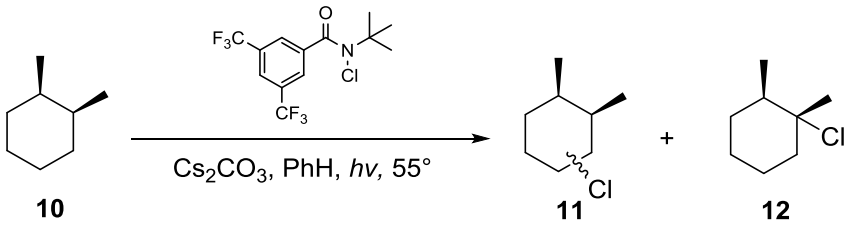


Table 3-9. Chlorination of 1,2 *trans*-dimethylcyclohexane with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
3° trans	13.25	0.91
	14.17	20.32
	14.36	56.71
	15.07	19.41
	16.48	2.63



1,2-*cis*-dimethylcyclohexane: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (50.0 mg, 0.143 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (140 μL). 1,2-*cis*-dimethylcyclohexane (30.5 μL, 0.143 mmol), and cesium carbonate (46.6 mg, 0.143 mmol) were then added.. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 2 hours at 55°. Upon completion, the reaction mixture was concentrated under reduced pressure and dissolved in pentanes. The resulting suspension was run through a plug of silica and concentrated a second time. The reaction was analyzed by NMR using 2,5-dimethylfuran as an internal standard to determine the yield of secondary bromide products. GC analysis was used to determine the relative amount and yield, of the tertiary bromide products. 72.9% NMR yield of combined chloride products.

Figure 3-10. Overlaid gas chromatogram for chlorination of 1,2 *cis*-dimethylcyclohexane with authentic 3^{o} products

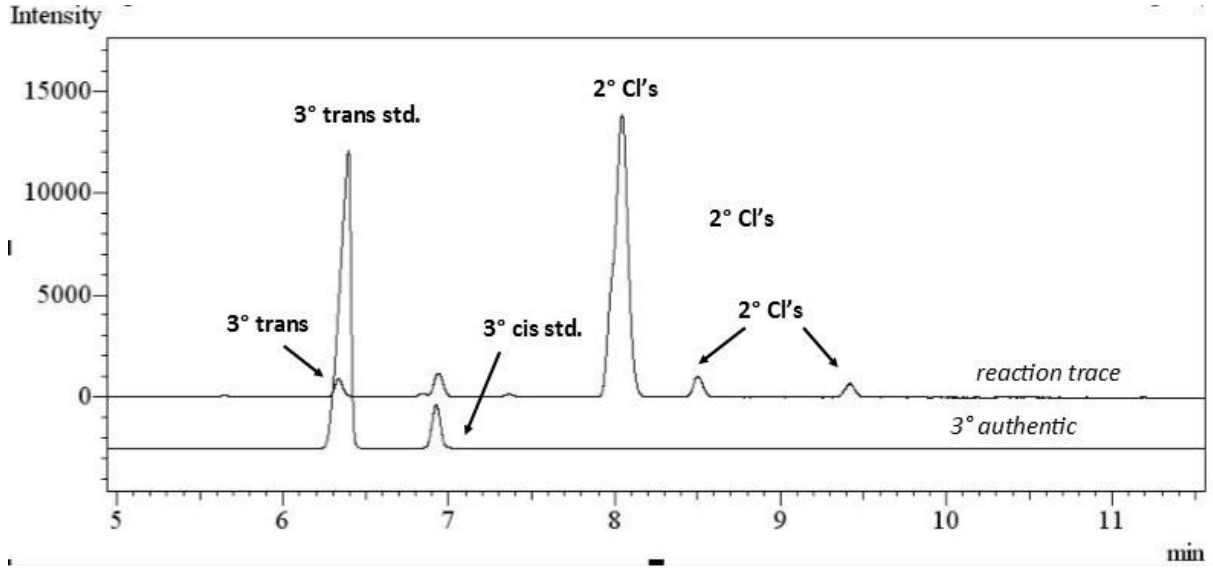
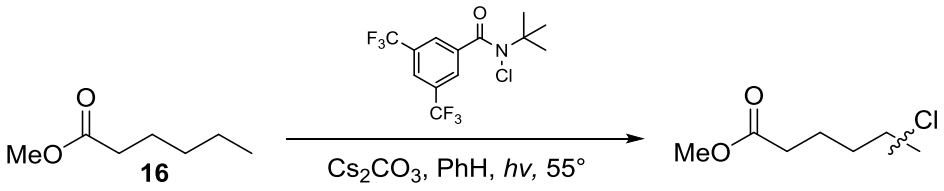


Table 3-10. Chlorination of 1,2 *cis*-dimethylcyclohexane with chloroamide 1

Chlorination of 1,2 *cis*-dimethylcyclohexane: Selectivity		
Product	Retention Time	Percent Area
3° trans	6.34	3.32
3° cis	6.94	4.81
	8.04	85.56
	8.52	4.30
	9.42	2.98

Chlorination of Electron Withdrawing Alkanes



Methyl hexanoate: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (100.0 mg, 0.286 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (560 μL). Methyl hexanoate (21.2 μL, 0.143 mmol), and cesium carbonate (93.2 mg, 0.286 mmol) were then added. *Note: alkane was added as a stock solution in benzene to improve the reproducibility of the results.* The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 83.2% GC yield of combined chloride products. *Only the major isomer was synthesized independently. The secondary chloride products were assigned via analogy to our C-H bromination chemistry.*

Figure 3-11. Overlaid gas chromatogram for chlorination of methylhexanoate with authentic δ product.

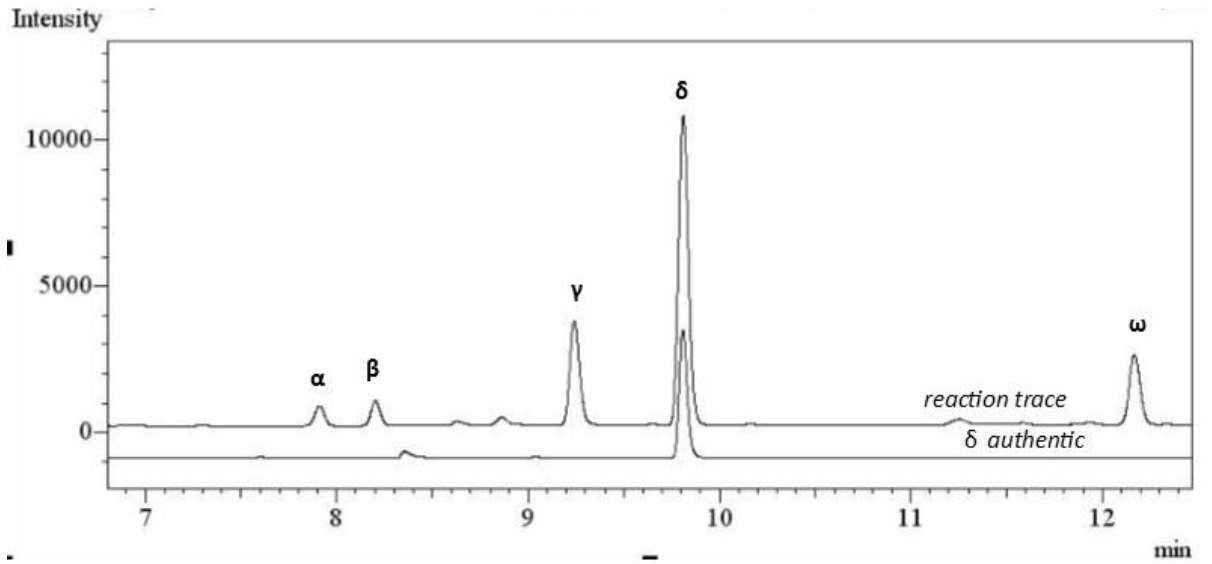
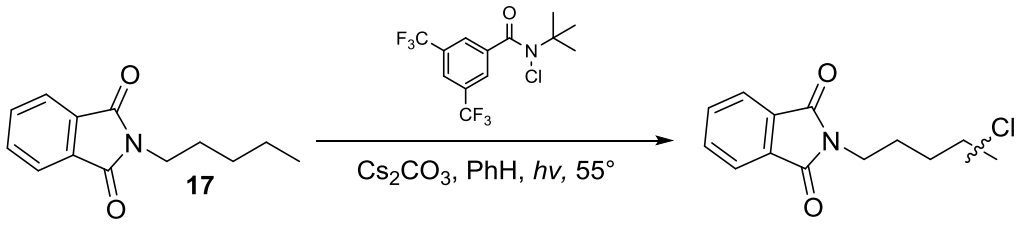


Table 3-11. Chlorination of methylhexanoate with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	7.91	3.64
β	8.20	4.62
γ	9.24	19.67
δ	9.81	57.63
ω	12.16	14.41

The response factors for all isomers of chloro-Methylhexanoate were calculated to be nearly identical; therefore, the relative percent area of the product peaks reflects the relative amounts of the different isomers formed in the reaction.



N-Penthylphthalimide: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (100.0 mg, 0.286 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (280 μL). *N*-Pentylphthalimide (31.0 mg, 0.143 mmol), and cesium carbonate (93.4 mg, 0.143 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 79.7% GC yield of combined chloride products. *Only the major isomer was synthesized independently. The secondary chloride products were assigned via analogy to our C-H bromination chemistry.*

3.6.3.1 Figure 3-12. Overlaid chromatogram for chlorination of *N*-pentylphthalimide with authentic δ product.

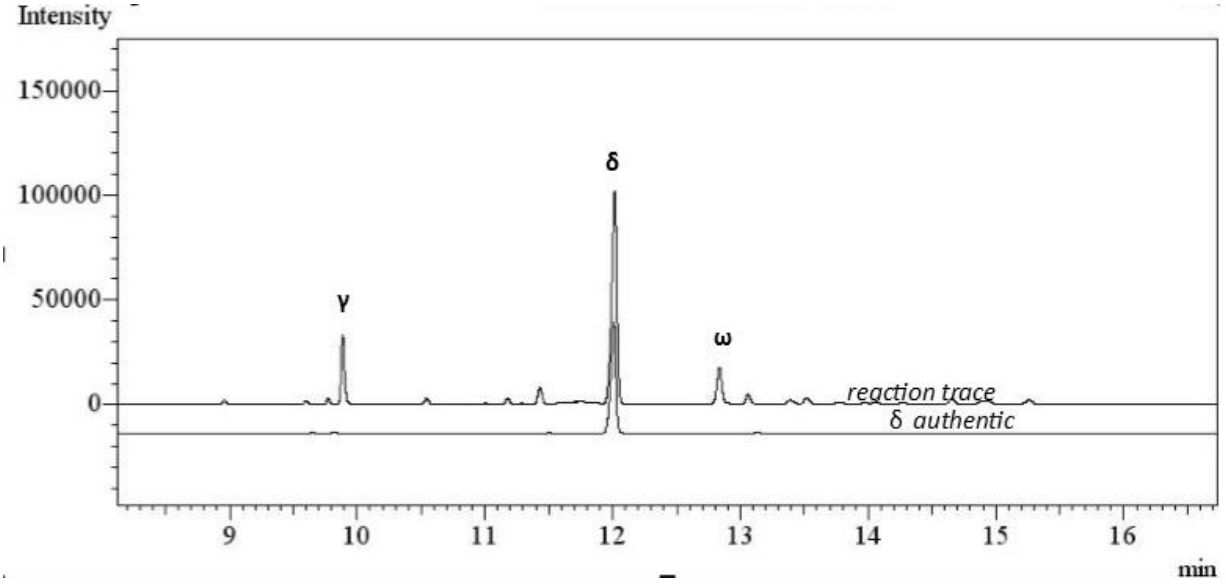
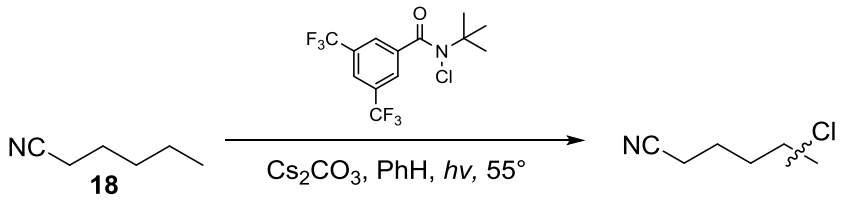


Table 3-12. Chlorination of *N*-pentylphthalimide with chloroamide 1

Chromoatogram Data Selectivity		
Product	Retention Time	Percent Area
α	----	----
β	----	----
γ	11.43	4.77
δ	12.02	81.35
ω	12.84	13.87



Hexanenitrile: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (100.0 mg, 0.286 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed

benzene (280 μL). Hexanenitrile (17.2 μL, 0.143 mmol), and cesium carbonate (93.8 mg, 0.286 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 78.6% GC yield of combined chloride products. *Only the major isomer was synthesized independently. The secondary chloride products were assigned via analogy to our C-H bromination chemistry.*

Figure 3-13. Overlaid chromatogram for chlorination of hexanenitrile with authentic δ product

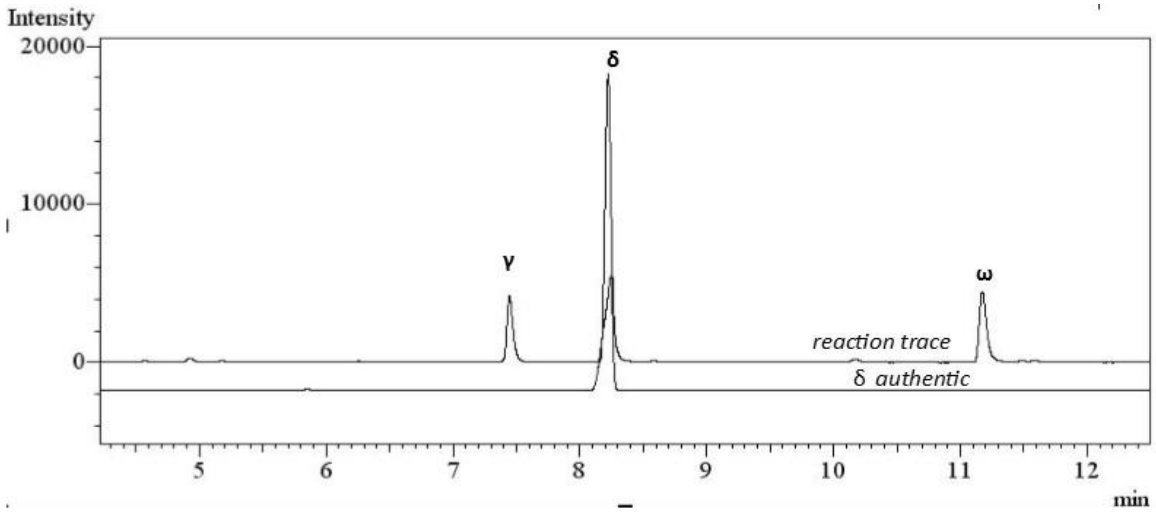
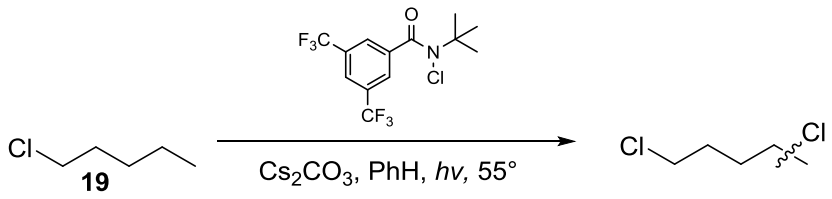


Table 3-13. Chlorination of hexanenitrile with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	---	---
β	---	---
γ	11.17	15.32
δ	12.81	73.93
ω	14.66	10.74



1-Chlorohexane: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (100.0 mg, 0.286 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (280 μL). 1-Chlorohexane (17.3 μL, 0.143 mmol), and cesium carbonate (93.0 mg, 0.286 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 74.0% GC yield of combined chloride products. *Only the major isomer was synthesized independently. The secondary chloride products were assigned via analogy to our C-H bromination chemistry.*

Figure 3-14. Overlaid chromatogram for chlorination of 1-chloropentane with authentic δ product

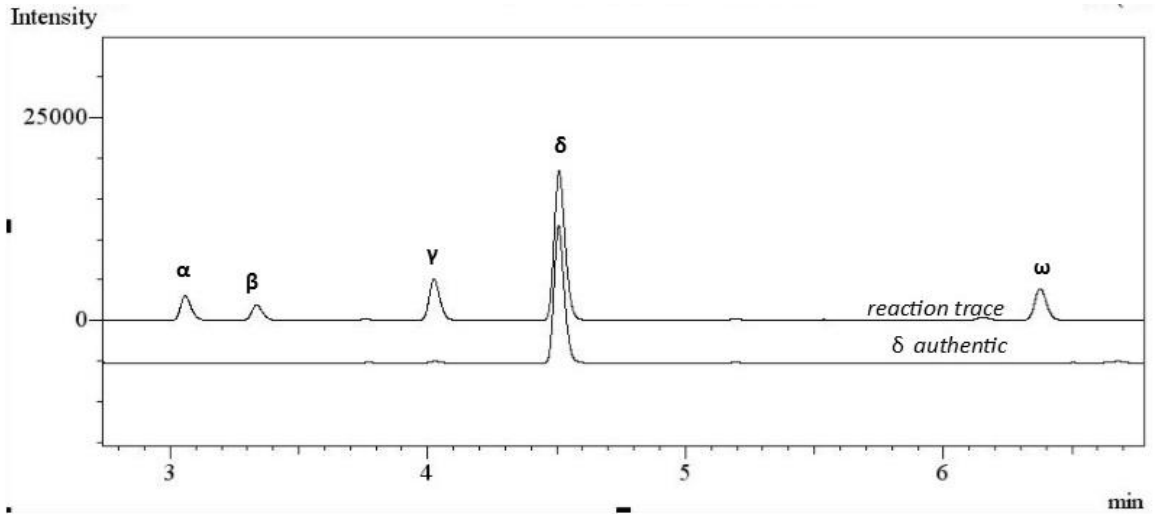
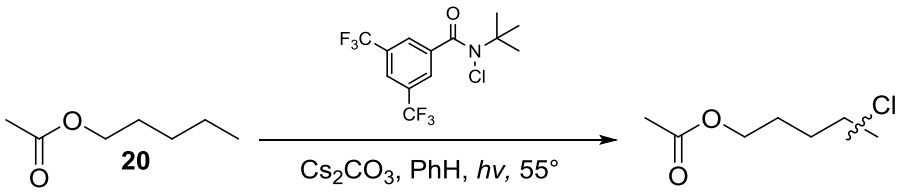


Table 3-14. Chlorination of 1-chloropentane with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	3.06	9.03
β	3.37	5.54
γ	4.02	15.29
δ	4.51	57.23
ω	6.37	12.91



Amyl Acetate: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (100.0 mg, 0.286 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (280 μL). Amyl acetate (21.3 μL, 0.143 mmol), and cesium carbonate (93.1 mg, 0.286 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 89.4% GC yield of combined chloride products. *Only the major isomer was synthesized independently. The secondary chloride products were assigned via analogy to our C-H bromination chemistry.*

Figure 3-15. Overlaid chromatogram for chlorination of amylacetate with authentic δ product

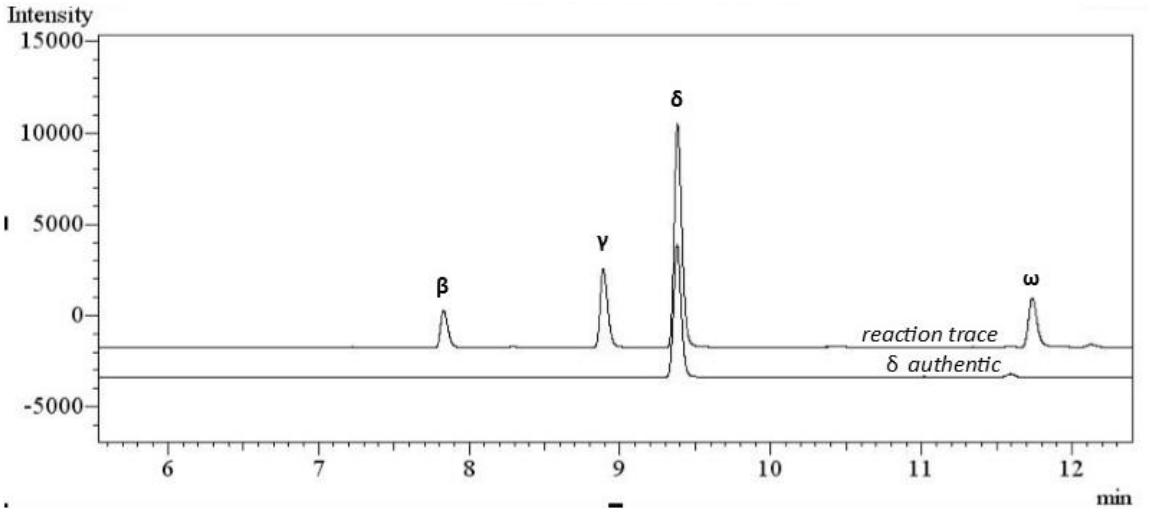
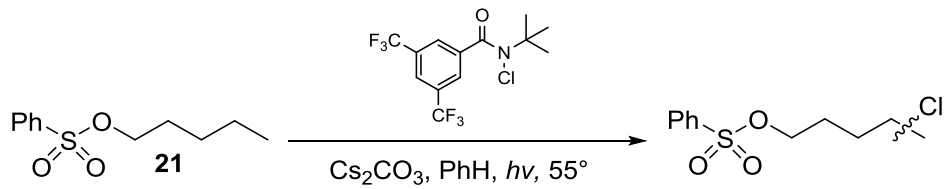


Table 3-15. Chlorination of amyl acetate with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	---	---
β	7.83	8.9
γ	8.88	19.69
δ	9.83	57.85
ω	11.73	13.47



Pentyl Benzenesulfonate: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (100.0 mg, 0.286 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (280 μL). Pentyl benzenesulfonate (32.6 mg, 0.143 mmol), and cesium carbonate (92.5 mg, 0.286 mmol) were then added. The reaction was then sealed with teflon tape

and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 86.5% GC yield of combined chloride products. *Only the major isomer was synthesized independently. The secondary chloride products were assigned via analogy to our C-H bromination chemistry.*

Figure 3-16. Overlaid gas chromatogram for chlorination of pentyl benzene sulfonate with authentic δ product

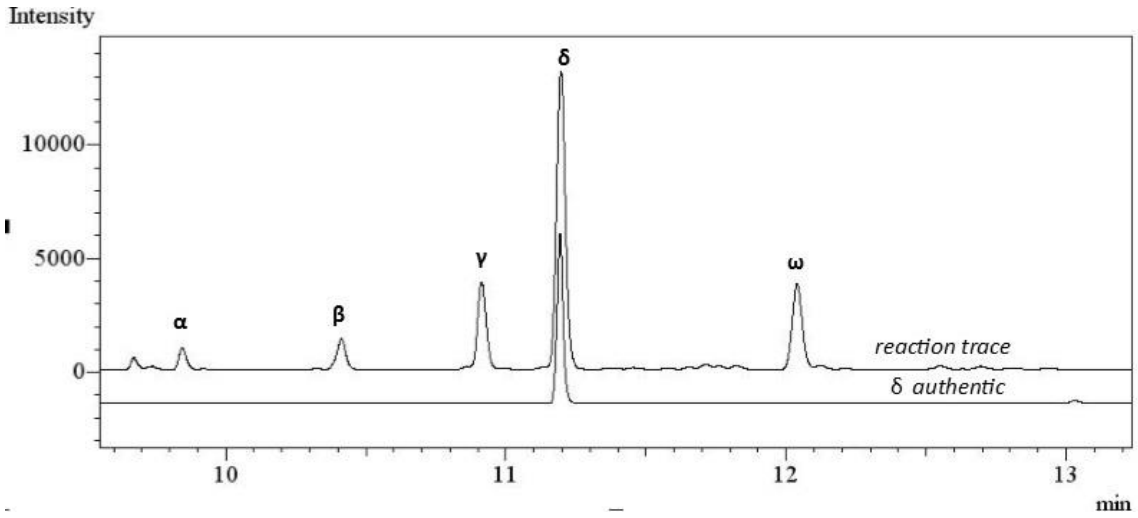
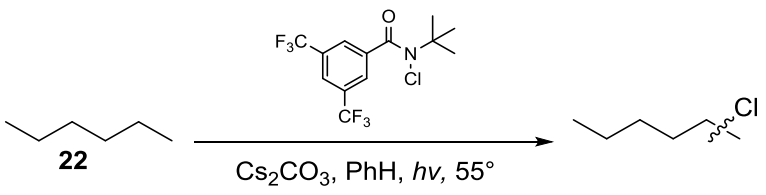


Table 3-16. Chlorination of pentyl benzene sulfonate with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	9.84	3.48
β	10.41	6.05
γ	10.91	16.13
δ	11.19	55.76
ω	12.04	18.57



n-Hexane: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (40.0 mg, 0.116 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (120 µL). n-Hexane (15.2 µL, 0.116 mmol), and cesium carbonate (37.8 mg, 0.116 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. 70.4% GC yield of combined chloride products. *Only the major isomer was synthesized independently. The secondary chloride products were assigned via analogy to our C-H bromination chemistry.*

Figure 3-17. Overlaid gas chromatogram for chlorination of *n*-hexane with authentic products

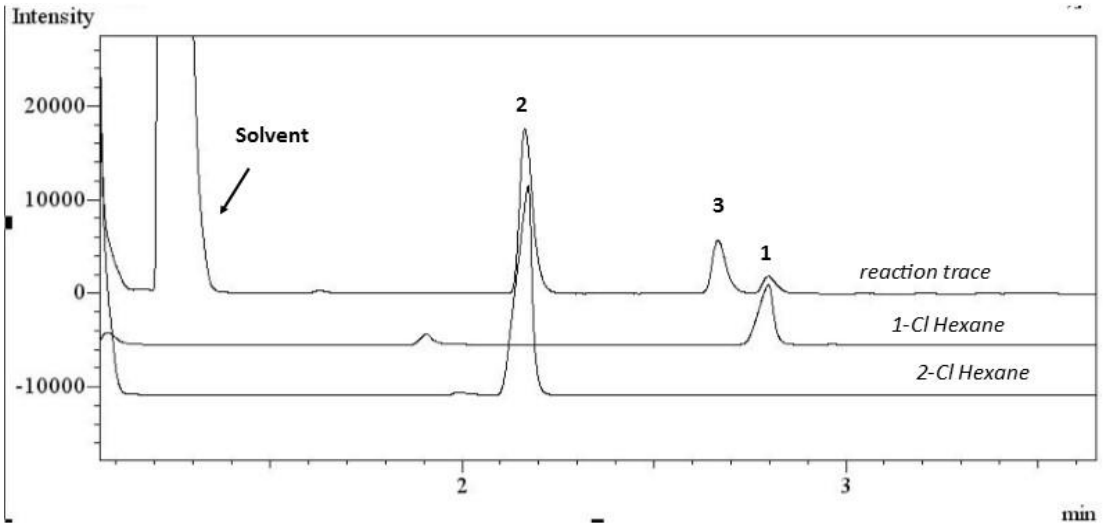
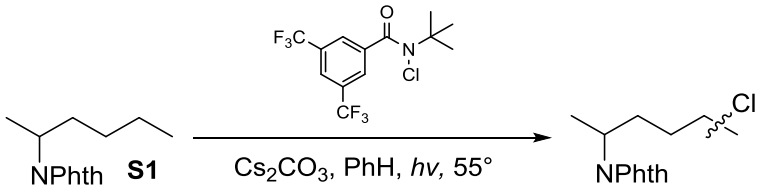


Table 3-17. Chlorination of *n*-hexane with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
2-Chlorohexane	2.16	69.51
3-Chlorohexane	2.66	23.38
1-Chlorohexane	2.79	7.10

Chlorination of in the Presence of More Reactive C-H Bonds and Substrate Unsaturation



S1: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (150.0 mg, 0.44 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (440 μL). The phthalimide substrate (50.2 mg, 0.22 mmol), and cesium carbonate (144.8 mg, 0.44 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The crude reaction mixture was purified using column chromatography (5% EtOAc/Hexane) to isolate a mixture of major chloride products for characterization. 1D selective TOCSY NMR experiments were used to determine the identity of the major products. Reaction yield (88%) was calculated from crude NMR spectra using 2,5 dimethylfuran as an internal standard.

Analytical Data for mixture of chloride products formed from **S1:** **^{1}H NMR** ^{1}H NMR (600MHz ,CHLOROFORM-d) δ = 7.91 - 7.80 (m, 2 H), 7.79 - 7.66 (m, 2 H), 4.44 - 4.28 (m, 1 H), 4.13 - 3.94 (m, 0.8 H), 3.51 (t, *J* = 6.6 Hz, 0.4 H), 2.33 (dtd, *J* = 4.4, 9.9, 14.0 Hz, 0.5 H), 2.25 - 2.07 (m, 1 H), 2.07 - 1.95 (m, 0.5 H), 1.89 (tdd, *J* = 5.4, 10.7, 13.8 Hz, 0.5 H), 1.84 - 1.69 (m, 1.5 H), 1.69 - 1.55 (m, 1.5 H), 1.55 - 1.43 (m, 6 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.5, 134.0, 133.9, 131.9, 131.8, 123.2, 123.1, 58.3, 57.9, 47.3, 47.2, 46.7, 44.8, 37.6, 37.2, 32.9, 32.1, 31.1,

30.7, 25.4, 25.3, 24.1, 18.8, 18.7 ppm; **IR** (thin film, cm^{-1}) 2954.1, 2928.2, 1771.2, 1713.2, 1455.4, 1435.8, 1400.0, 1189.4, 1031.1, 723.2; **HRMS** (ESI) Calcd. for $[C_{14}H_{16}ClNO_2+Na]^+$ = 288.08, Found = 288.08

Figure 3-18. Overlaid gas chromatogram for chlorination of substrate **S1** with isolated products

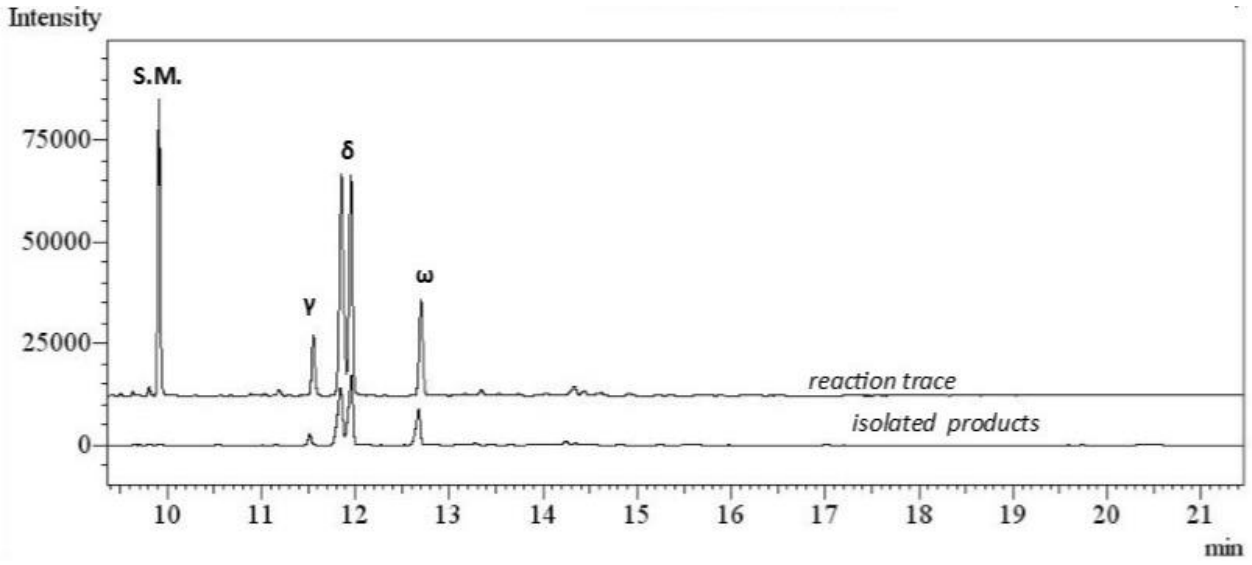
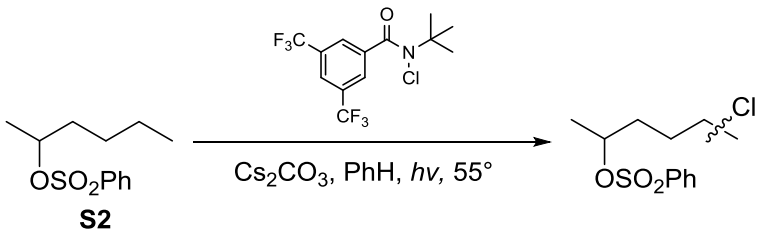


Table 3-18. Chlorination of phthalimide substrate S1 with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	---	---
β	---	---
γ	11.51	8.72
δ	11.81	42.75
δ	11.91	32.74
ω	12.04	18.57



Chlorination of S2: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (150.0 mg, 0.44 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (440 μL). The sulfonate substrate (52.9 mg, 0.22 mmol), and cesium carbonate (144.8 mg, 0.44 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The crude reaction mixture was purified using column chromatography (5% EtOAc/Hexane) to isolate a mixture of major chloride products for characterization. 1D selective TOCSY NMR experiments were used to determine the identity of the major products. Reaction yield (76%) was calculated from crude NMR spectra using 2,5 dimethylfuran as an internal standard.

Analytical Data for mixture of chloride products formed from **S2:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.96 - 7.91 (m, 2 H), 7.70 - 7.64 (m, 1 H), 7.60 - 7.53 (m, 2 H), 4.76 - 4.62 (m, 1 H), 3.98 - 3.85 (m, 0.8 H), 3.45 (t, *J* = 6.6 Hz, 0.2 H), 1.90 - 1.50 (m, 0.8 H), 1.47 - 1.43 (m, 3 H), 1.42 - 1.31 (m, 2 H), 1.30 - 1.25 (m, 3 H) **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 137.3, 133.7, 133.6, 129.4, 129.3, 129.2, 129.1, 127.9, 127.8, 127.7, 127.6, 80.5, 79.77, 37.7, 35.8, 35.1, 33.8, 33.3, 31.9, 25.4, 25.3, 21.0, 20.9 ppm; **IR** (thin film, cm^{-1}) 3010.3, 2926.0, 1777.3, 1710.3, 1448.9, 1452.0, 1400.8, 1387.4, 1190.2, 1033.0, 750.2; **HRMS** (ESI) Calcd. for $[C_{12}H_{17}ClSO_3+Na]^+$ = 288.05, Found = 299.05

Figure 3-19. Overlaid gas chromatogram for chlorination of substrate **S2** with isolated products

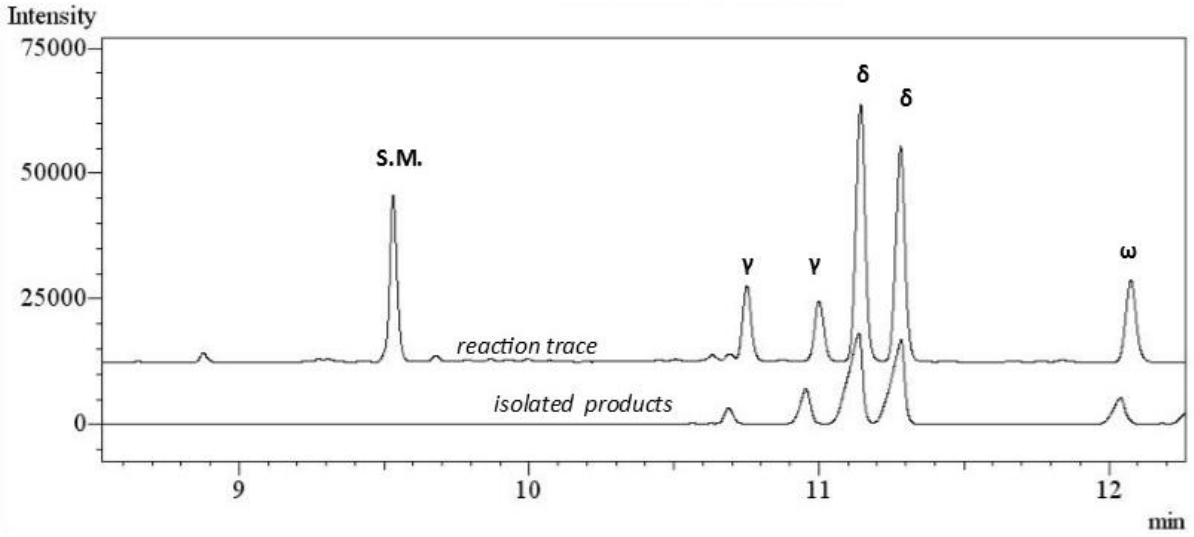
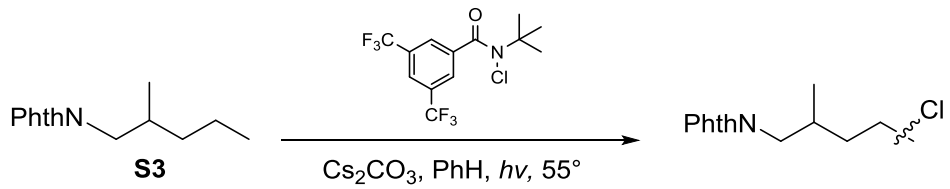


Table 3-19. Chlorination of sulfonate substrate S2 with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	---	---
β	---	---
γ	10.75	9.41
γ	11.00	8.90
δ	11.14	37.05
δ	11.28	31.23
ω	12.08	13.36



Chlorination of S3: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (150.0 mg, 0.44 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (440 μL). The phthalimide substrate (50.3 mg, 0.22 mmol), and cesium carbonate (144.8

mg, 0.44 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The crude reaction mixture was purified using column chromatography (5% EtOAc/Hexane) to isolate a mixture of major chloride products for characterization. 1D selective TOCSY NMR experiments were used to determine the identity of the major products. Reaction yield (69%) was calculated from crude NMR spectra using 2,5 dimethylfuran as an internal standard.

Analytical Data for mixture of chloride products formed from **S3:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.90 - 7.81 (m, 2 H), 7.78 - 7.69 (m, 13 H), 4.33 - 4.19 (m, 0.3 H), 4.11 (ddd, *J* = 3.5, 6.6, 10.5 Hz, 0.3 H), 3.70 - 3.63 (m, 0.3 H), 3.63 - 3.48 (m, 2 H), 2.33 (dtd, *J* = 3.5, 6.9, 13.6 Hz, 0.5 H), 2.28 - 2.20 (m, 0.3 H), 2.08 - 1.96 (m, 0.3 H), 1.96 - 1.85 (m, 3 H), 1.85 - 1.74 (m, 0.7 H), 1.74 - 1.66 (m, 1 H), 1.58 - 1.44 (m, 3 H), 1.01 - 0.91 (m, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.8, 168.7, 168.6, 134.1, 134.0, 133.9, 133.8, 132.0, 131.9, 131.8, 123.3, 123.2, 56.2, 56.1, 45.2, 45.1, 44.7, 43.9, 43.8, 43.0, 32.2, 31.5, 30.8, 30.7, 30.6, 29.9, 26.1, 25.2, 18.1, 17.4, 16.7 ppm; **IR** (thin film, cm^{-1}) 3013.0, 2926.0, 1780.7, 1703.1, 1458.2, 1452.9, 1382.8, 1374.2, 1210.0, 1058.1, 701.2; **HRMS** (ESI) Calcd. for $[C_{14}H_{16}ClNO_2+Na]^+$ = 288.07, Found = 288.08

Figure 3-20. Overlaid chromatogram for chlorination of substrate **S3** with isolated products

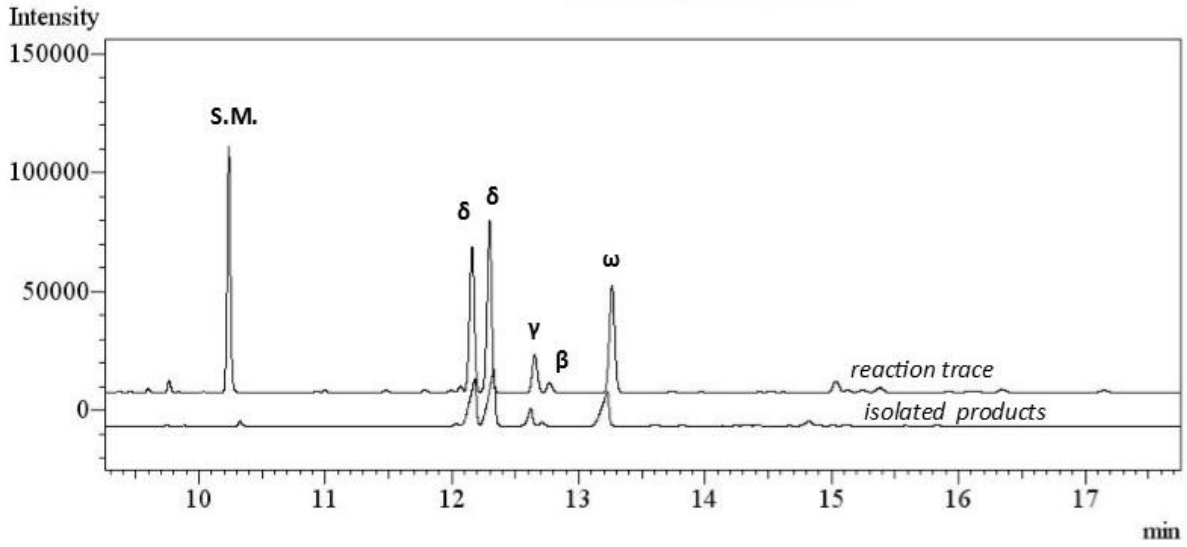
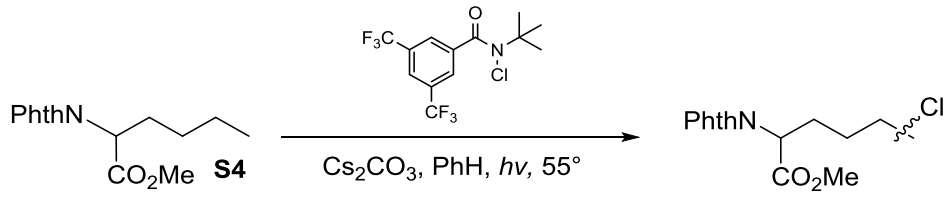


Table 3-20. Chlorination of phthalimide substrate **S3** with chloroamide 1

Chlorination of Phthalimide Substrate **S3**: Selectivity		
Product	Retention Time	Percent Area
α	---	---
β	12.77	2.05
γ	12.65	8.17
δ	12.96	29.96
δ	11.28	36.36
ω	13.27	25.49



Chlorination of S4: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (150.0 mg, 0.44 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (440 μL). The phthalimide substrate (58.2 mg, 0.22 mmol), and cesium carbonate (144.8

mg, 0.44 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The crude reaction mixture was purified using column chromatography (10-20% EtOAc/Hexane) to isolate a mixture of major chloride products for characterization. 1D selective TOCSY NMR experiments were used to determine the identity of the major products. Reaction yield (66%) was calculated from crude NMR spectra using 2,5 dimethylfuran as an internal standard.

Analytical Data for mixture of chloride products formed from **S4:** **^{1}H** (600MHz ,CHLOROFORM-d) δ = 7.96 - 7.86 (m, 2 H), 7.83 - 7.72 (m, 2 H), 4.92 - 4.81 (m, 1 H), 4.13 - 3.97 (m, 0.8 H), 3.79 - 3.72 (m, 3 H), 3.52 (t, *J* = 6.6 Hz, 0.4 H), 2.59 - 2.49 (m, 0.5 H), 2.47 - 2.38 (m, 0.8 H), 2.38 - 2.23 (m, 1 H), 1.88 - 1.76 (m, 4 H), 1.74 - 1.65 (m, 1 H), 1.54 - 1.45 (m, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 169.5, 169.4, 167.7, 167.6, 167.5, 134.4, 134.3, 131.7, 123.7, 123.6, 123.5, 57.8, 57.4, 52.9, 52.8, 51.9, 51.4, 44.5, 37.0, 36.7, 36.6, 31.7, 28.0, 26.4, 26.1, 25.4, 25.3, 23.6 ppm; **IR** (thin film, cm^{-1}) 3102.6, 2987.4, 2929.2, 1779.3, 1751.0, 1710.5, 1526.6, 1446.9, 1342.3, 1309.3, 1275.3, 882.9, 758.4, 719.4; **HRMS** (ESI) Calcd. for $[C_{25}H_{16}ClNO_4+Na]^+$ = 332.07, Found = 332.06

Figure 3-21. Overlaid chromatogram for chlorination of substrate **S4** with isolated products

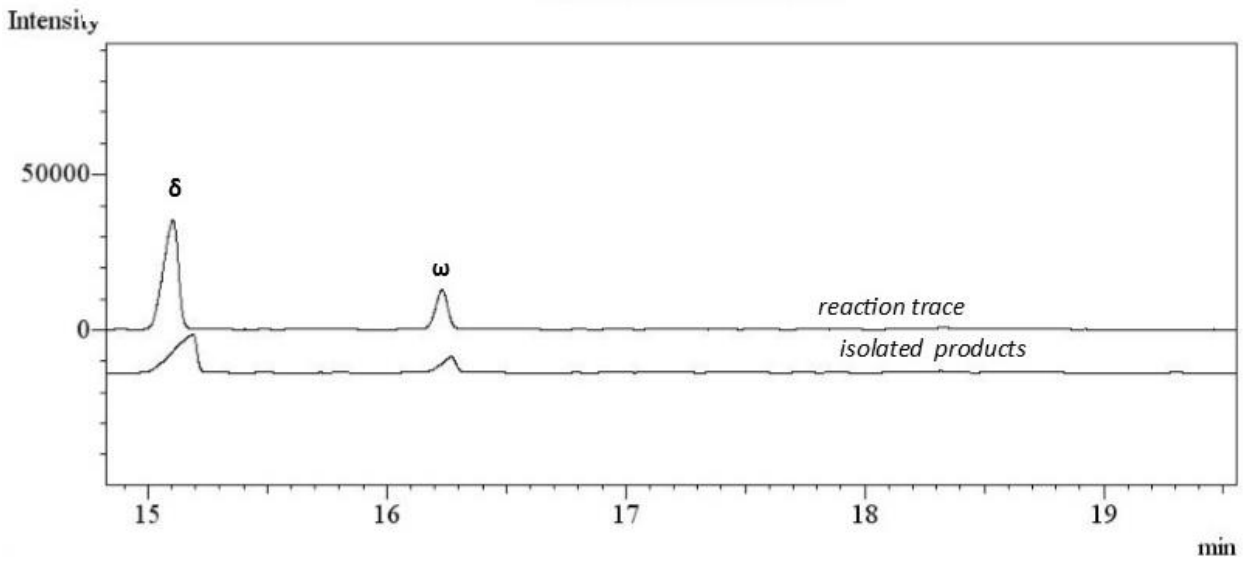
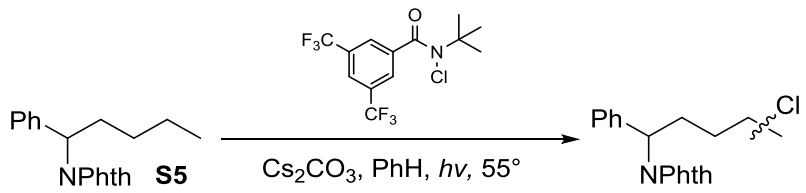


Table 3-21. Chlorination of phthalimide substrate S4 with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	---	---
β	---	---
γ	---	---
δ	15.14	77.54
ω	16.23	22.45



Chlorination of S5: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (150.0 mg, 0.44 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (440 μL). The phthalimide substrate (64.1 mg, 0.22 mmol), and cesium carbonate (144.8 mg, 0.44 mmol) were then added. The reaction was then sealed with teflon tape and taken out of

the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The crude reaction mixture was purified using column chromatography (5% EtOAc/Hexane) to isolate a mixture of major chloride products for characterization. 1D selective TOCSY NMR experiments were used to determine the identity of the major products. Reaction yield (81%) was calculated from crude NMR spectra using 2,5 dimethylfuran as an internal standard.

Analytical Data for mixture of chloride products formed from **S5:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.85 - 7.80 (m, 2 H), 7.74 - 7.68 (m, 2 H), 7.60 - 7.54 (m, 2 H), 7.39 - 7.33 (m, 2 H), 7.32 - 7.25 (m, 1 H), 5.40 - 5.29 (m, 1 H), 4.19 - 4.02 (m, 0.8 H), 3.53 (t, *J* = 6.6 Hz, 0.4 H), 2.88 - 2.74 (m, 0.3 H), 2.74 - 2.55 (m, 1 H), 2.55 - 2.41 (m, 0.4 H), 1.88 (qd, *J* = 7.0, 13.9 Hz, 0.3 H), 1.83 - 1.70 (m, 0.5 H), 1.56 - 1.49 (m, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.4, 168.3, 168.2, 139.5, 139.3, 129.2, 134.1, 124.0, 133.9, 131.8, 131.7, 128.8, 128.7, 128.6, 128.2, 128.1, 128.0, 127.9, 127.8, 123.4, 123.3, 123.2, 58.2, 57.9, 54.9, 54.8, 45.4, 44.7, 37.7, 37.8, 37.6, 34.7, 32.1, 31.6, 30.3, 28.4, 28.1, 25.4, 25.3, 24.4, 22.7, 14.2 ppm; **IR** (thin film, cm^{-1}) 3022.4, 2959.2, 2929.3, 2859.4, 1769.3, 1710.9, 1463.7, 1397.1, 1072.3, 884.1, 757.5, 721.2; **HRMS** (ESI) Calcd. for $[C_{19}H_{18}ClNO_2+Na]^+$ = 350.09, Found = 350.10

Figure 3-22. Overlaid chromatogram for chlorination of substrate **S5** with isolated products

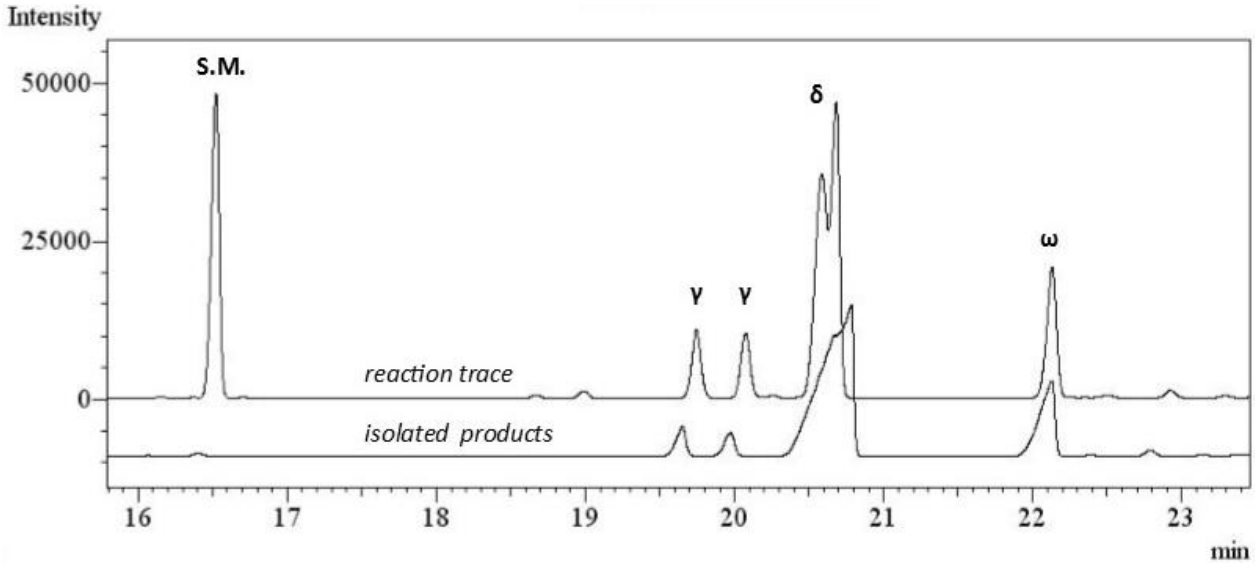
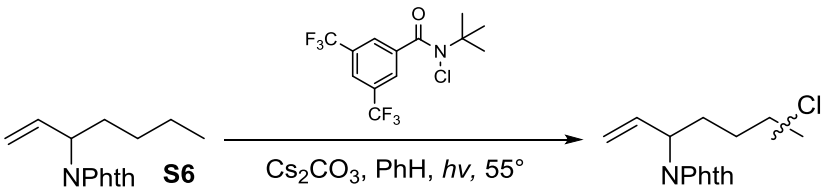


Table 3-22. Chlorination of phthalimide substrate S5 with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	---	---
β	---	---
γ	19.74	8.06
γ	20.07	7.68
δ	20.58	34.94
δ	20.68	32.90
ω	22.13	16.41



Chlorination of S6: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (150.0 mg, 0.44 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed

benzene (440 μL). The phthalimide substrate (52.8 mg, 0.22 mmol), and cesium carbonate (144.8 mg, 0.44 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly analyzed by gas chromatography using dodecane as an internal standard. The crude reaction mixture was purified using column chromatography (5% EtOAc/Hexane) to isolate a mixture of major chloride products for characterization. 1D selective TOCSY NMR experiments were used to determine the identity of the major products. Reaction yield (78%) was calculated from crude NMR spectra using 2,5 dimethylfuran as an internal standard.

Analytical Data for mixture of chloride products formed from **S6:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 7.87 - 7.83 (m, 2 H), 7.77 - 7.71 (m, 2 H), 6.33 - 6.19 (m, 1 H), 5.33 - 5.17 (m, 2 H), 4.81 - 4.68 (m, 1 H), 4.13 - 3.96 (m, 1 H), 3.52 (t, *J* = 6.6 Hz, 0.5 H), 2.39 - 2.26 (m, 0.7 H), 2.26 - 2.03 (m, 3 H), 2.03 - 1.88 (m, 0.5 H), 1.88 - 1.70 (m, 3 H), 1.70 - 1.60 (m, 2 H), 1.55 - 1.43 (m, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 168.1, 135.4, 135.3, 134.1, 134.0, 131.8, 123.3, 123.2, 118.0, 112.9, 58.0, 57.9, 53.9, 53.8, 53.5, 44.7, 37.2, 37.0, 32.0, 31.2, 29.3, 29.2, 25.4, 25.3, 23.8 ppm; **IR** (thin film, cm^{-1}) 2938.4, 2864.1, 1463.1, 1448.2, 1363.5, 1127.1, 1007.2, 980.4, 962.2, 824.4, 751.8, 684.9, 591.0; **HRMS** (ESI) Calcd. for $[C_{15}H_{16}ClNO_2+Na]^+$ = 300.07, Found = 300.08

Figure 3-23. Overlaid chromatogram for chlorination of substrate **S6** with isolated products

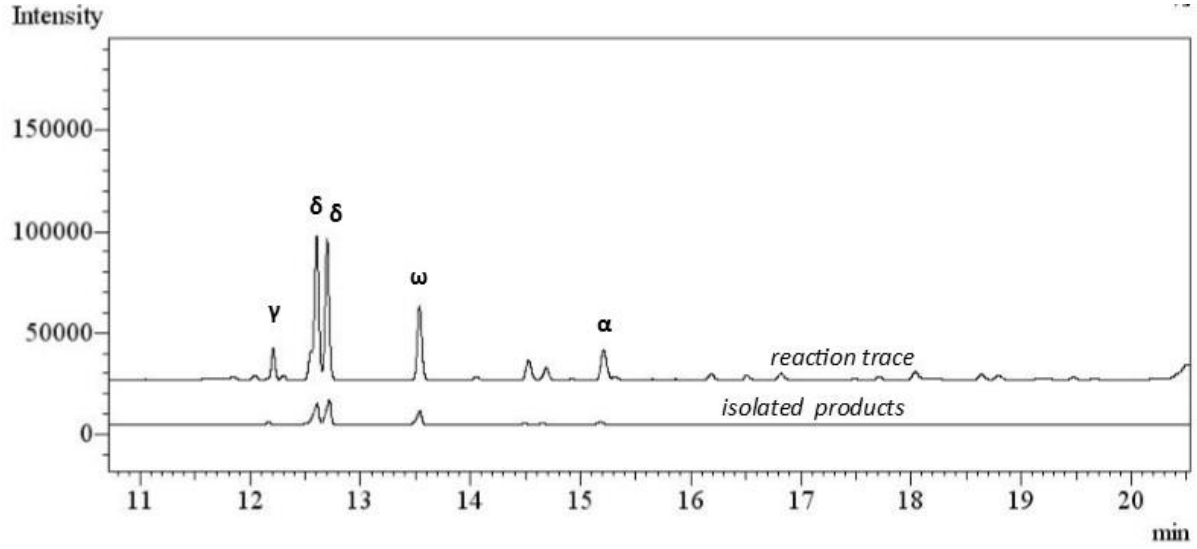
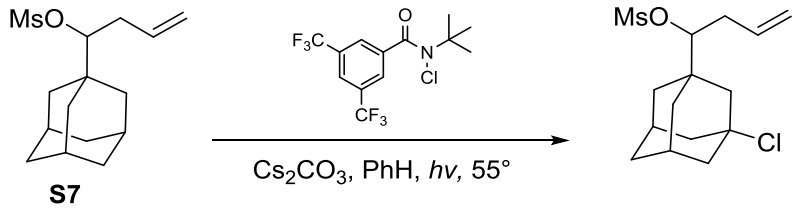


Table 3-23. Chlorination of phthalimide substrate S6 with chloroamide 1

Chromatogram Data Selectivity		
Product	Retention Time	Percent Area
α	15.14	8.99
β	---	---
γ	12.13	36.32
δ	12.53	28.77
δ	12.63	19.28
ω	13.46	8.99

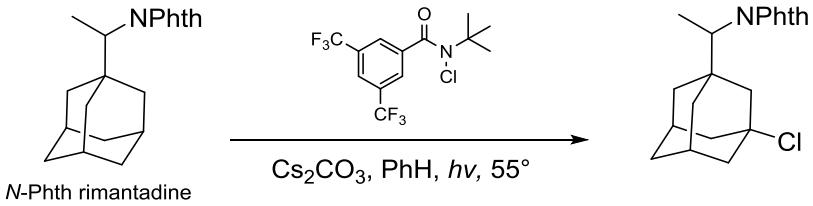
Chlorination of Complex Substrates



Chlorination of S7: A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (160.0 mg, 0.46 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed

benzene (950 μL). The adamantane substrate (130.4 mg, 0.46 mmol), and cesium carbonate (150.s mg, 0.46 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. The crude reaction mixture was purified using column chromatography (5% EtOAc/Hexane) to isolate a single isomer of product (95 mg, 0.29 mmol, 65% yield) as a white solid.

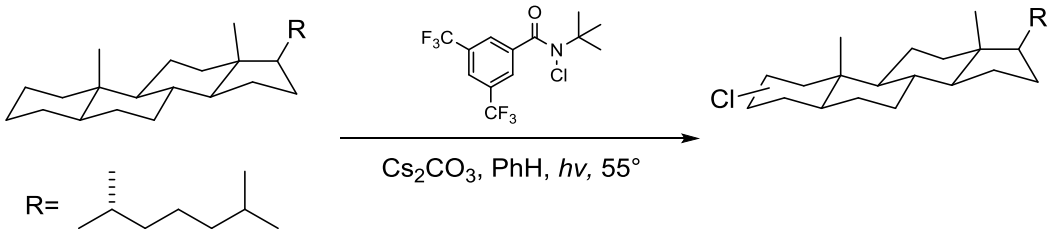
Analytical Data for single chloride product formed from **S7:** **^{1}H NMR** (600MHz ,CHLOROFORM-d) δ = 5.96 - 5.81 (m, 1 H), 5.26 - 5.09 (m, 2 H), 4.47 (dd, *J* = 2.9, 9.4 Hz, 1 H), 3.09 - 2.98 (m, 3 H), 2.61 - 2.49 (m, 1 H), 2.41 (td, *J* = 8.9, 15.1 Hz, 1 H), 2.34 - 2.20 (m, 2 H), 2.17 - 2.10 (m, 2 H), 2.10 - 1.94 (m, 4 H), 1.76 - 1.49 (m, 7 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 134.7, 118.7, 89.4, 67.8, 47.6, 46.9, 46.8, 41.1, 39.3, 36.9, 36.5, 34.7, 34.1, 31.0, 30.9 ppm; **IR** (thin film, cm^{-1}) 2933.2, 2858.1, 2254.4, 1774.2, 1710.5, 1612.2, 1451.2, 1355.7, 1170.6, 1108.9, 1036.5, 912.2, 879.4, 835.0, 724.1, 531.3; **HRMS** (ESI) Calcd. for $[C_{15}H_{23}ClSO_3+Na]^+$ = 341.10, Found = 341.09



Rimantadine (30): A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (300.0 mg, 0.88 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (950 μL). The phthalimide substrate (272.3 mg, 0.22 mmol), and cesium carbonate (286.1 mg, 0.88 mmol) were then added. The reaction was then sealed with teflon tape and taken out of

the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. The crude reaction mixture was purified using column chromatography (5% EtOAc/Hexane) to isolate a single isomer of product (199 mg, 0.58 mmol, 66% yield) as a white solid. NMR of the crude reaction mixture showed a small amount of dichloride formed (10:1 mono:di).

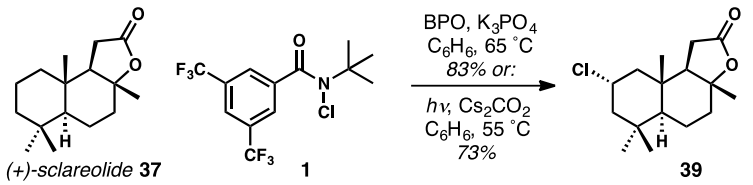
Analytical Data for **31:** **^{1}H NMR**^{1}H NMR (600MHz ,CHLOROFORM-d) δ = 7.89 - 7.79 (m, 2 H), 7.77 - 7.62 (m, 2 H), 4.11 (q, *J* = 7.5 Hz, 1 H), 2.26 - 2.16 (m, 2 H), 2.11 - 1.90 (m, 6 H), 1.70 - 1.53 (m, 6 H), 1.51 (d, *J* = 7.3 Hz, 3 H); **^{13}C NMR** (125MHz ,CHLOROFORM-d) δ = 169.2, 169.1, 134.1, 133.9, 132.1, 131.4, 123.4, 123.1, 68.6, 55.6, 49.4, 46.9, 46.8, 42.1, 37.8, 37.6, 34.8, 31.4, 31.3, 11.96 ppm; **IR** (thin film, cm^{-1}) 2935.1, 2888.9, 1709.5, 1642.1, 1333.5, 1172.5, 905.4, 835.9, 791.6, 736.7, 539.0; **HRMS** (ESI) Calcd. for $[C_{20}H_{22}BrNO_2+H]^+$ = 366.12, Found = 366.12



Chlorination of Cholestane (32): A flame-dried, 1 dram vial was charged with a stir bar and chloroamide (80.0 mg, 0.23 mmol) in the dark (overhead lights in the laboratory turned off), fitted with a PTFE lined screw cap and the reaction was taken into a glovebox, and dissolved in of dry, freeze-pump-thawed benzene (800 μL). The alkane substrate (88.3 mg, 0.23 mmol), and cesium carbonate (72.3 mg, 0.23 mmol) were then added. The reaction was then sealed with teflon tape and taken out of the glovebox and irradiated with two 23W compact fluorescent light bulbs for 4 hours at 55°. Upon completion, the reaction mixture was diluted with DCM (3 mL) and directly

analyzed by gas chromatography using dodecane as an internal standard. NMR of the crude reaction mixture was compared to existing literature data to determine the yield (75%) and selectivity of the reaction. The analytical data was consistent with the literature.[35]

3.6.4 Synthesis of Chlorolissoclimide: Experimental Procedures

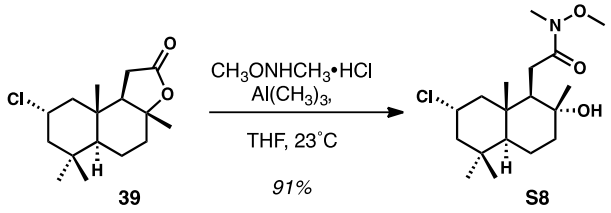


2-Chlorosclareolide 39. (+)-Sclareolide **37** (1.00 g, 3.99 mmol, 1.0 equiv), benzoyl peroxide (165 mg, 0.68 mmol, 0.17 equiv), K_3PO_4 (144 mg, 0.68 mmol, 0.17 equiv), and chloroamide **1** (3.5 g, 10.0 mmol, 2.5 equiv) were dissolved in benzene (13 mL) and the mixture was degassed for 20 min with an Ar balloon bearing a 18 gauge needle. A reflux condenser was attached to the flask and the mixture was heated at reflux for 24 h. A 30 μL aliquot revealed a ~50% conversion (^{1}H NMR). The reaction mixture was cooled to ambient temperature and more benzoyl peroxide (100 mg, 0.41 mmol, 0.10 equiv) and K_3PO_4 (87 mg, 0.41 mmol, 0.10 equiv) were added. The solution was degassed in the same manner and heated for 16 h after which aliquot NMR revealed ~75% conversion. This process was repeated again and after another 15 h no sclareolide remained. The mixture was concentrated under a stream of air. Direct chromatographic purification (SiO_2, 10% EtOAc in hexanes) afforded a clear amorphous solid (941 mg, 3.31 mmol, 83% yield). Our data match those previously reported by Groves.[35]

Alternative Procedure Using Light as the Radical Initiator: (+)-Sclareolide **37** (600 mg, 2.39 mmol, 1.0 equiv), Cs_3CO_3 (780 mg, 2.39 mmol, 1.0 equiv), and chloroamide **1** (1.74 g, 5.0 mmol,

2.1 equiv) were dissolved in degassed benzene in the glovebox (5 mL). The mixture was stirred and irradiated with 2 - 23W CFL bulbs (1650 lumens each) at 55 ˚C for 36 h (when ^{1}H NMR revealed ~95% conversion). The mixture was filtered and concentrated under reduced pressure. Direct chromatographic purification (SiO_2, 5-10% EtOAc in hexanes) afforded a clear amorphous solid (535 mg, 3.9 mmol, 78% yield) Another 22mg were present in the mixed fractions to give a total of 557mg (81.6% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.22 (tt, *J* = 12.2, 4.2 Hz, 1H), 2.43 (dd, *J* =16.2, 14.8 Hz, 1H), 2.29 (dd, *J* = 16.2, 6.5 Hz, 1H), 2.13 (dt, *J* = 12.0, 3.3 Hz, 1H), 1.98–2.07 (m, 2H), 1.91 (dq, *J* = 14.4, 3.3 Hz, 1H), 1.70 (td, *J* = 12.4, 4.3 Hz, 1H), 1.54 (t, *J* = 12.7 Hz, 1H), 1.32–1.42 (m, 2H), 1.33 (s, 3H), 1.13 (dd, *J* = 12.7, 2.7 Hz, 1H), 0.972 (s, 3H), 0.968 (s, 3H), 0.90 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 176.0, 85.8, 58.6, 55.7, 53.8, 52.4, 49.7, 38.4, 38.2, 35.8, 32.9, 28.6, 21.6, 21.3, 20.1, 15.8; **IR** (film) 2951, 2871, 1773, 1387, 1197 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{16}H_{25}O_2Cl$ $[M]^+$: 284.1543; found 284.1548; **$[\alpha]^{25}_D$** +48.2˚ (*c* = 1.00, $CHCl_3$).

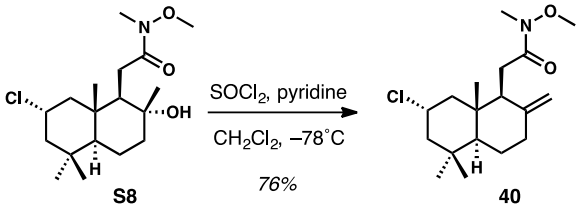


Amide S8. (Note: The following two-step sequence to make **40** is based on the procedures for the non-chlorinated variant reported by Boukouvalas[36] with slight modifications.) $Al(CH_3)_3$ (2.0 M in toluene, 3.50 mL, 6.99 mmol, 2.1 equiv) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (647 mg, 6.66 mmol, 2.0 equiv) in CH_2Cl_2 (12 mL) at 0˚C. The white suspension became a clear solution. The ice bath was removed and after 2 h a solution of **39** (950 mg, 3.33 mmol, 1.0 equiv in 12 mL CH_2Cl_2)

was added dropwise over ~5 min at ambient temperature. After stirring for 2 hours at 23 ˚C, the flask was cooled in an ice bath and 5 mL of 10% aq. H_2SO_4 was added.

The ice bath was removed and the crude mixture was diluted with CH_2Cl_2 (40 mL), H_2O (10 mL), and 1M HCl (30 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 X 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 70%→80% EtOAc in hexanes) to afford amide **S8** as a thick clear oil (1.05 g, 3.04 mmol, 91% yield).

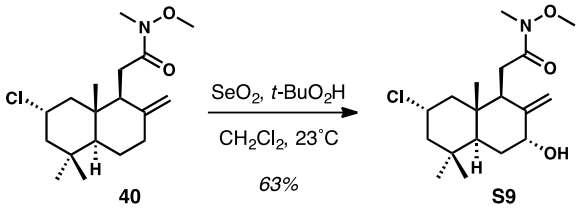
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.17 (tt, *J* = 12.3, 4.0 Hz, 1H), 3.74 (s, 1H), 3.20 (s, 1H), 2.58 (d, *J* = 16.1 Hz, 1H), 2.48 (dd, *J* = 16.4, 6.7 Hz, 1H), 2.08 (ap d, *J* = 10.9, 1H), 2.03 (dd, *J* = 6.5, 3.6 Hz, 1H), 1.92–1.98 (m, 2H), 1.69 (dq, *J* = 13.8, 2.4 Hz, 1H), 1.50 (t, *J* = 12.7 Hz, 1H), 1.47 (dd, *J* = 13.3, 3.9 Hz, 1H), 1.32 (t, *J* = 12.2 Hz, 1H), 1.26 (qd, *J* = 13.2, 3.2 Hz, 1H) 1.16 (s, 1H), 1.09 (dd, *J* = 12.3, 2.0 Hz, 1H), 0.95 (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 175.5, 72.7, 61.3, 56.3, 55.8, 55.1, 54.9, 51.9, 49.6, 44.1, 41.0, 35.9, 33.1, 27.0, 23.4, 21.8, 20.1, 16.5; **IR** (film) ν 3500, 2966, 2927, 1655, 1454, 1340, 1158 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{18}H_{32}O_3ClNa$ $[M + Na]^+$: 368.1968; found 368.1963; **$[\alpha]^{25}_D$** +32.9˚ (*c* = 1.00, $CHCl_3$).



Alkene 40. Alcohol **S8** (510 mg, 1.46 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL). Pyridine (236 µL, 2.92 mmol, 2.0 equiv) was added, and the solution was cooled to –78 ˚C. Pyridine (969 µL, 12.0 mmol, 8.25 equiv) was added to a conical flask containing $SOCl_2$ (530 µL, 7.30 mmol, 5 equiv) and CH_2Cl_2 (15 mL) and this clear mixture was transferred via Teflon® cannula dropwise over 15 min to the flask containing alcohol **S8**. The reaction was complete after 45 min at –78 ˚C and sat. aq. $NaHCO_3$ (20 mL) was added. The product mixture was warmed to ambient temperature, the phases were separated and the aqueous phase

was extracted (2 x 30 mL CH_2Cl_2). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The pale yellow crude oil was purified by flash column chromatography (SiO_2, 11% EtOAc in hexanes) to afford alkene **40** as a thick oil (364 mg, 1.11 mmol, 76% yield).

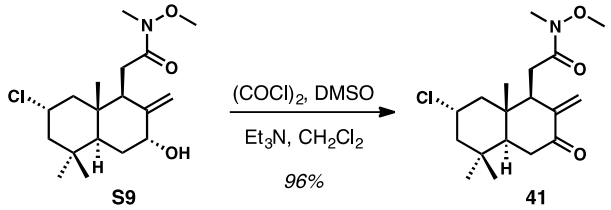
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.48 (s, 1H), 4.17 (tt, *J* = 12.3, 3.9 Hz, 1H), 3.73 (s, 3H), 3.16 (s, 3H), 2.72 (dd, *J* = 15.0, 10.7 Hz, 1H), 2.58 (d, *J* = 10.1 Hz, 1H), 2.37–2.42 (m, 2H), 2.09–2.18 (m, 2H), 1.98 (ddd, *J* = 12.8, 3.7, 2.2 Hz, 1H), 1.70–1.76 (m, 1H), 1.55 (t, *J* = 12.6 Hz, 1H), 1.50 (t, *J* = 12.2 Hz, 1H), 0.97 (s, 3H), 0.85 (s, 3H), 0.79 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.1, 148.3, 107.0, 61.4, 55.8, 53.9, 52.0, 51.4, 49.3, 41.2, 37.1, 36.1, 33.3, 32.5, 24.1, 23.4, 22.2, 15.3; IR (film) ν 2939, 2852, 1776, 1667, 1461, 1385, 1004 cm^{-1}; **HRMS** (ESI) *m/z* calc'd for $C_{18}H_{30}O_2ClNNa$ $[M + Na]^+$ 350.1863, found 350.1866; **$[\alpha]^{25}_D$** +7.38° (*c* = 1.00, $CHCl_3$).



Allylic Alcohol S9. A solution of *t*-butyl hydroperoxide (133 μL, 5.5 M in decane, 730 μmol, 4.4 equiv) was added to an ice cold stirring suspension of selenium dioxide (5.5 mg, 49.8 μmol, 0.3 equiv) in CH_2Cl_2 (2.5 mL). After 30 min, a solution of amide **40** (54.4 mg, 166 μmol, 1.0 equiv) was added dropwise and the solution was allowed to warm to room temperature. TLC analysis indicated complete consumption of starting material after 8 h. The excess peroxide was quenched with sat. aq. Na_2SO_3. The biphasic solution was diluted with water (5 mL) and CH_2Cl_2 (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. The crude oil was

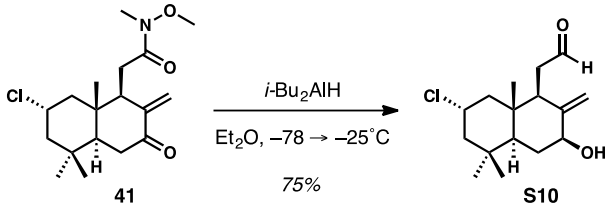
purified by column chromatography (SiO_2, 80% EtOAc in hexanes) to give alcohol **S9** as a white amorphous solid (36.4 mg, 105 μmol, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.61 (s, 1H), 4.37 (s, 1H), 4.17 (tt, *J* = 12.3, 3.9 Hz, 1H), 3.74 (s, 3H), 3.16 (s, 3H), 3.06 (d, *J* = 10.8 Hz, 1H), 2.68 (dd, *J* = 15.8, 10.9 Hz, 1H), 2.42 (dd, *J* = 16.1, 3.3 Hz, 1H), 2.13 (ap d, *J* = 12.1 Hz, 1H) 2.00 (ddd, *J* = 12.8, 3.8, 2.1 Hz, 1H), 1.91 (dt, *J* = 13.9, 2.7 Hz, 1H), 1.84 (dd, *J* = 12.9, 2.9 Hz, 1H), 1.60 (t, *J* = 12.6 Hz, 1H), 1.56 (t, *J* = 12.2 Hz, 1H), 1.48 (td, *J* = 13.4, 3.1 Hz, 1H), 0.98 (s, 3H), 0.87 (s, 3H), 0.76 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.5, 149.6, 110.2, 77.2, 73.1, 61.4, 55.7, 52.0, 49.0, 46.2, 46.0, 41.3, 35.7, 32.4, 33.0, 29.8, 26.7, 22.1, 14.4; **IR** (film) ν 3405, 2960, 2939, 2897, 1645, 1460, 1436, 1389, 766 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{18}H_{30}O_3ClNNa$ $[M + Na]^+$: 366.1812, found 366.1818; **$[\alpha]^{25}_D$** –25.7˚ (*c* = 0.60, $CHCl_3$).



Enone 41. A solution of oxalyl chloride (16.7 μL, 192 μmol, 1.2 equiv) in CH_2Cl_2 (800 μL) was cooled to –78 ˚C and DMSO (27 μL, 384 μmol, 2.4 equiv) was added. After 10 min alcohol **S9** (55 mg in 800 μL CH_2Cl_2, 160 μmol, 1.0 equiv) was added dropwise over 10 min. The solution was stirred for 20 min and Et_3N (111.5 μL, 800 μmol, 5 equiv) was added. The suspension was allowed to warm to 0 ˚C. After 40 min at 0 ˚C no starting material was present by TLC analysis and the mixture was diluted with hexanes (5 mL) and sat. aq. NH_4Cl (5 mL). The biphasic solution was further diluted with 1:1 hexanes in EtOAc (15 mL) and water. The organic phase was washed sequentially with brine (10 mL) and water (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash column chromatography (SiO_2, 35% EtOAc in hexanes) gave **41** as a thick oil (53 mg, 154 μmol, 96% yield).

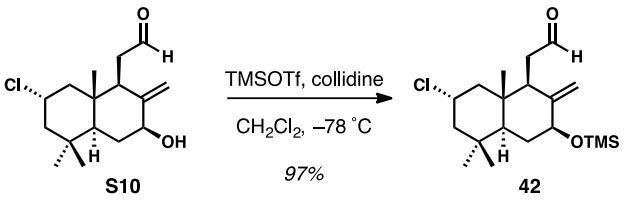
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (d, *J* = 2.5 Hz, 1H), 5.11 (d, *J* = 2.4 Hz, 1H), 4.18 (tt, *J* = 12.4, 3.8 Hz, 1H), 3.74 (s, 3H), 3.19 (s, 3H), 2.97–3.03 (m, 1H), 2.58–2.72 (m, 3H), 2.28 (dd, *J* = 17.9, 14.1 Hz, 1H), 2.23 (ap d *J* = 12.5 Hz, 1H), 2.05 (ddd, *J* = 12.9, 3.7, 2.2 Hz, 1Hz), 1.73 (dd, *J* = 14.0, 4.6 Hz, 1H), 1.60 (t, *J* = 12.7 Hz, 1H), 1.56 (t, *J* = 12.3 Hz, 1H), 0.96 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.6, 146.8, 121.1, 72.1 61.5, 54.6, 51.6, 49.8, 49.6, 48.9, 39.5, 37.5, 36.0, 32.7, 32.3, 28.9, 21.4, 15.1; **IR** (film) ν 2963, 1693, 1662, 1608, 1461, 1415, 1388, 1264 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{18}H_{28}O_3ClNNa$ $[M + Na]^+$: 364.1655, found 364.1658; **$[\alpha]^{22}_D$** –36.3˚ (*c* = 0.51, $CHCl_3$).



Aldehyde S10. Enone **41** (72 mg, 205 μmol, 1.0 equiv) was dissolved in Et_2O (4 mL, 0.05 M) and the solution was cooled to –78˚C, forming a suspension. A solution of *i*Bu_2AlH in toluene (1.0 M, 615 μL, 615 μmol, 3.0 equiv) was added slowly along the side of the flask and the reaction mixture became homogenous. After 40 min at –78 ˚C, the flask was warmed to –25 ˚C over 1 h then stirred at that temperature. After 1.5 h acetone (50 μL) was added followed by 1M HCl (1 mL). The biphasic solution was warmed to ambient temperature and 1M HCl (3 mL) and water (3 mL) were added. The aqueous phase was extracted (3 x 6 mL 1:1 EtOAc in hexanes) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The crude oil was purified by chromatography (SiO_2, 22%→27% EtOAc in hexanes) to afford **S10** as a thick oil (44 mg, 154 μmol, 75% yield).

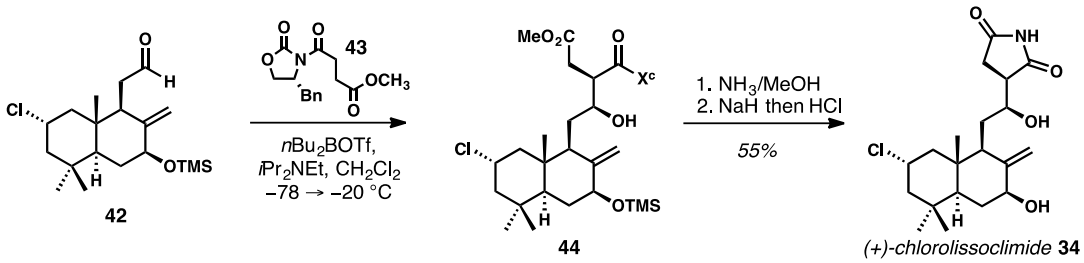
^{1}H NMR (500 MHz $CDCl_3$) δ 9.66 (d, *J* = 3.0 Hz, 1H) 5.23 (s, 1H), 4.62 (s, 1H), 4.16 (tt, *J* = 12.3, 4.0 Hz, 1H), 4.10 (br s, 1H), 2.63 (ddd, *J* = 17.0, 11.1, 3.0 Hz, 1H), 2.48 (dd, *J* = 17.0, 3.5 Hz, 1H), 2.41 (ap d, *J* = 11.0 Hz, 1H), 2.07–2.14 (m, 3H), 2.02 (ddd, *J* = 13.0, 3.9, 2.1 Hz, 1H), 1.86 (d, *J* = 4.1 Hz, 1H), 1.55 (t, *J* = 12.7 Hz, 1H), 1.41 (t, *J* = 12.2 Hz, 1H), 1.23–1.32 (m, 2H), 1.00 (s, 3H), 0.88 (s, 3H), 0.75 (s, 3H); **^{13}C**

NMR(125 MHz, $CDCl_3$) δ 201.6, 149.3, 105.9, 72.97, 55.0, 51.84, 51.76, 49.4, 48.5, 40.7, 39.3, 35.9, 33.2, 32.7, 22.1, 15.1; **IR** (film) ν 3400, 2960, 2853, 2725, 1720, 1647, 1459, 1391 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{16}H_{25}O_2ClNH_4$ $[M + NH_4]^+$: 302.1887, found 302.1882. $\mathbf{[\alpha]^{22}_D}$ –18.1˚ (*c* = 1.0, $CHCl_3$).



TMS ether 42. Aldehyde **S10** (12.5 mg, 43 μmol, 1.0 equiv) was dissolved in CH_2Cl_2 (450 μL) and cooled to –78 ˚C. To the reaction mixture were sequentially added 2,4,6-collidine (57 μL, 430 μmol, 10 equiv) and TMSOTf (47 μL, 258 μmol, 6.0 equiv). After 1 h at –78 ˚C, triethylamine (50 μL) and methanol (100 μL) were added and the flask was warmed to ambient temperature. The solution was diluted with 10% EtOAc in hexanes (5 mL) and washed consecutively with water, citric acid (10% aq.), and brine (4 mL each). The organic extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give aldehyde **42** a thin clear film (14.5 mg, 40.6 μmol, 97% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (d, *J* = 2.8 Hz, 1H), 5.25 (s, 1H), 4.58 (s, 1H), 4.15 (tt, *J* = 12.2, 3.8 Hz, 1H), 4.02 (ap dd, *J* = 10.1, 5.2 Hz, 1H), 2.62 (ddd, *J* = 16.8, 10.9, 3.1 Hz, 1H), 2.46 (dd, *J* = 16.8, 3.5 Hz, 1H), 2.39 (ap d, *J* = 10.6 Hz, 1H), 2.08 (ap d, *J* = 12.1 Hz, 1H), 2.03 (ddd, *J* = 12.9, 3.9, 2.0 Hz, 1H), 1.93 (ddd, *J* = 11.9, 4.2, 1.7 Hz, 1H), 1.54 (t, *J* = 12.7 Hz, 1H), 1.39 (t, *J* = 11.9 Hz, 1H), 1.32 (ap t, *J* = 11.1 Hz, 1H), 1.29 (t, *J* = 15.1 Hz, 1H), 0.98 (s, 3H), 0.87 (s, 3H), 0.75 (s, 3H), 0.13 (s, 9H); **^{13}C NMR**(125 MHz, $CDCl_3$) δ 201.8, 148.5, 107.0, 73.5, 55.1, 51.9, 51.8, 49.5, 48.6, 40.7, 39.4, 35.8, 33.6, 33.1, 22.1, 15.1, –0.1; **IR** (film) ν 2956, 2851, 2718, 1726, 1650, 1460, 1393, 1251 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{19}H_{33}O_2ClSiNH_4$ $[M + NH_4]^+$: 374.2282, found 374.2285; $\mathbf{[\alpha]_D^{22}}$ –8.60˚ (*c* = 1.10, $CHCl_3$).



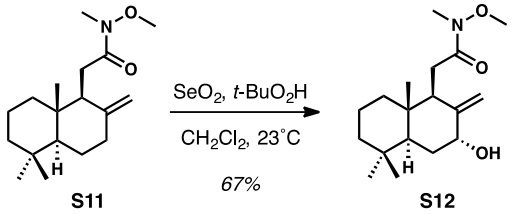
Chlorolissoclimide 34. Imide **43**[37] (14.0 mg, 48 μmol, 1.3 equiv) was dried by azeotropic distillation from of benzene (20 μL) in a 1 dram vial and dissolved in CH_2Cl_2 (250 μL, 0.1 M). The solution was cooled to –78 ˚C and *n*Bu_2BOTf (1.0 M in CH_2Cl_2, 52 μL, 52 μmol, 1.4 equiv) was added along the side of the vial. The clear solution was stirred at –78 ˚C for 30 min. At that temperature, *i*Pr_2NEt (1.0 M in CH_2Cl_2, 67 μL, 67 μmol, 1.8 equiv) was added and the mixture was stirred for 20 min. To ensure complete enolization, the vial was warmed to 0 ˚C for 30 sec and cooled back to –78 ˚C. The solution often becomes pale yellow upon warming but remained clear. Finally, a solution of aldehyde **42** (13.2 μg in 100 μL CH_2Cl_2, 37 μmol, 1.0 equiv) was added at –78 ˚C and the reaction vial was warmed over 1.5 hours to –25 ˚C and a temperature between –30 and –25 ˚C was maintained for 20 h. The reaction mixture was quenched with methanol (50 μL) warmed to ambient temperature, and water (3 mL) and CH_2Cl_2 (3 mL) were added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield crude product **44** a yellow oil.

The crude aldol product was transferred to a 1 dram vial, NH_3 (2.0 M in methanol, 800 μL) was added, and the reaction was stirred at 23 ˚C for 24 h. The solution was concentrated *in vacuo* to afford a mixture of chlorolissoclimide (**34**), and the primary amide of methyl ester **44**. To complete succinimide formation, the crude material was dissolved in dry THF (400 μL) and NaH (55% suspension in mineral oil, 3.5 mg, 80 μmol) was added at ambient temperature. The solution evolved bubbles for ~10 min. Water (200 μL) was added followed by 1M HCl (100 μL). The solution was quickly added to a mixture of pH 7 buffer (2 mL), brine (1 mL), and water (1 mL) and extracted with CH_2Cl_2 (4 x 4 mL CH_2Cl_2). The combined

organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatrography (SiO_2, 60%→70% EtOAc in hexanes) afforded a modestly (~85%) pure product. To further purify the product, this mixture was taken up in CH_2Cl_2 (250 μL) and hexanes was added until a white precipitate formed (~300 μL). The suspension was centrifuged for 1 min and the solvent was decanted with a pipette, leaving pure chlorolissoclimide (**34**) as a white film (7.8 mg, 20.3 μmol, 55% yield).

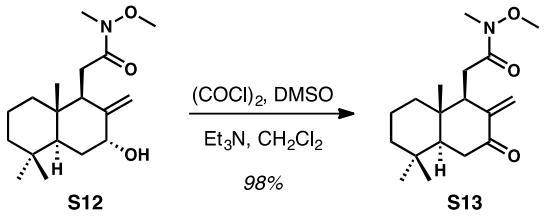
The data obtained for our synthetic sample of **34** matched those reported by Biard. For ^{1}H NMR and ^{13}C NMR data comparison to natural **34** in CD_2Cl_2 see Table S18, below.[38]

^{1}H NMR (500 MHz $CDCl_3$) δ 8.88 (br s, 1H), 5.30 (s, 1H), 4.90 (s, 1H), 4.29 (br s, 1H), 4.17 (tt, *J* = 12.2, 3.9 Hz, 1H), 4.00 (s, 1H), 3.03 (d, *J* = 3.2 Hz, 1H), 2.88–2.95 (m, 1H), 2.85 (dd, *J* = 18.0, 5.0 Hz, 1H), 2.68 (dd, *J* = 18.0, 9.2 Hz, 1H), 2.61 (br s, 1H), 2.20 (, *J* = 10.5 Hz, 1H), 2.09 (dd, *J* = 10.3, 4.8 Hz, 1H), 2.02 (d, *J* = 10.9 Hz, 1H), 1.82 (ddd, *J* = 13.2, 11.6, 5.3 Hz, 1H), 1.69 (s, 1H), 1.55–1.63 (m, 1H), 1.52 (t, *J* = 12.7 Hz, 1H), 1.23–1.28 (m, 2H), 1.20 (t, *J* = 14.2 Hz, 1H), 0.99 (s, 3H), 0.87 (s, 3H), 0.74 (s, 3H); **^{13}C NMR**(125 MHz, $CDCl_3$) δ 178.4, 176.0, 149.6, 105.5, 73.3, 68.9, 55.0, 52.2, 51.9, 51.7, 49.4, 46.7, 41.6, 35.9, 33.2, 33.1, 29.3, 29.0, 22.0, 15.0; **IR** (film) ν 2972, 2951, 1773, 1709, 1647, 1538, 1461, 1368 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{20}H_{30}O_4ClNH_4$ $[M + Na]^+$: 406.1761, found 406.1756. **$[\alpha]^{22}_D$** +50˚ (*c* = 0.11, CH_3OH), [lit.: $[\alpha]_D^{25}$ +119.3˚ (c = 1.59, CH_3OH)].



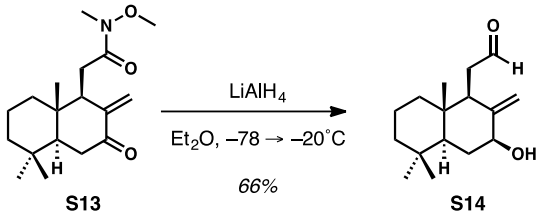
Alcohol S12. Weinreb amide **S11** (115 mg, 392 μmol) was subjected to the reaction conditions described above for **S9** to provide alcohol **S12** (81.4 mg, 263 μmol, 67% yield) as a thick oil after column chromatography (SiO_2, 80% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.56 (s, 1H), 4.36 (t, *J* = 2.3 Hz, 1H), 3.72 (s, 3H), 3.15 (s, 3H), 2.98 (d, *J* = 10.7 Hz, 1H), 2.64 (t, *J* = 5.3 Hz, 1H), 2.45 (dd, *J* = 16.3, 3.4 Hz, 1H), 1.89 (dt, *J* = 13.9, 2.8 Hz, 1H), 1.77 (dd, *J* = 13.2, 2.8 Hz, 1H), 1.59–1.47 (m, 4H), 1.43 (d, *J* = 11.4 Hz, 1H) 1.27–1.18 (m, 2H), 0.90 (s, 3H), 0.82 (s, 3H), 0.71 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.4, 150.7, 109.1, 73.5, 61.3, 47.2, 46.2, 41.9, 39.0, 38.6, 33.2, 33.0, 32.4, 30.4, 27.8, 21.6, 19.3, 13.8; **IR** (film) ν 3412, 2928, 1644, 1459, 1441, 1387 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{18}H_{31}NO_3Na$ $[M + Na]^+$: 332.2202; found 332.2202; **$[\alpha]^{25}_D$** –29.9° (*c* = 0.46, $CHCl_3$).



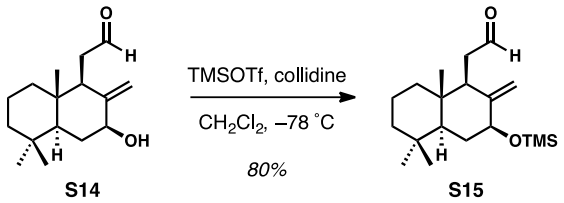
Enone S13. Alcohol **S12** (140 mg, 450 μmol) was subjected to the reaction conditions described for **41** to provide alcohol **S13** (137 mg, 445 μmol, 98% yield) as an oil after flash column chromatography (SiO_2, 40% EtOAc in hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.05 (s, 1H), 3.71 (s, 3H), 3.15 (s, 3H), 2.92 (s, 1H), 1.71–1.66 (m, 2H), 1.60, (dt, *J* = 13.6, 3.2 Hz, 1H), 1.57 (m, 1H), 1.48 (d, *J* = 13.4 Hz, 1H), 1.27–1.19 (m, 3H), 0.89 (s, 6H), 0.85 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 202.0, 173.6, 147.9, 119.7, 61.4, 60.3, 50.7, 50.1, 41.5, 38.5, 38.1, 37.1, 33.4, 32.5, 28.7, 20.9, 18.8, 14.4; **IR** (film) ν 2927, 1693, 1664, 1607, 1460.1, 1414, 1387 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{18}H_{29}NO_3Na$ $[M + Na]^+$: 330.2045; found 330.2038; **$[\alpha]^{23}_D$** –41.8° (*c* = 0.45, $CHCl_3$).



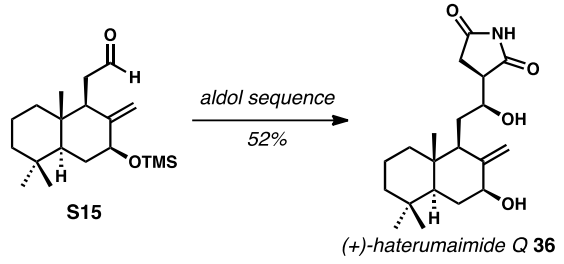
Aldehyde S14. Enone **S13** (20 mg, 65 μmol, 1 equiv) was azeotroped in a 1 dram vial from benzene (30 μL) then taken up in Et_2O (650 μL, 0.1 M). The clear solution was cooled to –78 °C to give a cloudy white suspension. A solution of $LiAlH_4$ (1M in Et_2O, 130 μmol, 130 μL, 2 equiv) was added dropwise down the side of the vial. After 3 h at –78 °C, no starting material remained by TLC analysis and 50 μL of EtOAc was added. The reaction mixture was warmed to –10 °C and water (10 μL) and 1M aq. NaOH (10 μL) were added sequentially followed by warming to room temperature. The reaction mixture was poured into ice water (5 mL) and extracted with (3 x 4 mL Et_2O). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude substance was purified by flash column chromatography (SiO_2, 25% EtOAc in hexanes) to aldehyde give **S14** as a clear oil (10.8 mg, 43 μmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (s, 1H), 4.58 (s, 1H), 4.09 (m, 1H), 2.56 (ddd, *J* = 16.8, 10.6, 3.1 Hz, 1H), 2.48 (dd, *J* = 16.8, 4.0 Hz, 1H), 2.14–2.11 (m, 1H), 1.77 (d, *J* = 5.3 Hz, 1H), 1.76–1.59 (m, 1H), 1.54–1.50 (m, 1H), 1.45 (d, *J* = 13.0 Hz, 1H), 1.34–1.26 (m, 2H), 1.22 (td, *J* = 13.1, 4.0 Hz, 1H), 1.06 (td, *J* = 12.6, 3.9 Hz, 1H), 0.93 (s, 3H), 0.83 (s, 3H), 0.70 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 202.8, 150.5, 104.8, 73.4, 52.8, 49.0, 41.8, 39.6, 39.1, 38.6, 33.45, 33.42, 21.6, 19.1, 14.5; **IR** (film) ν 3422, 2924, 2846, 2721, 1722, 1649, 1460, 1388 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{16}H_{26}O_2Na$ $[M + Na]^+$: 273.1830; found 273.1827; **$[\alpha]^{22}_D$** –15.3˚ (*c* = 0.2, $CHCl_3$)



TMS ether S15. Aldehyde **S14** (9.0 mg, 36 μmol) was subjected to the reaction conditions described for **42** and afforded TMS ether **S15** as a thin film (9.2 mg, 28 μmol, 80% yield) after flash column chromatrography (SiO_2, 5% EtOAc in hexanes).

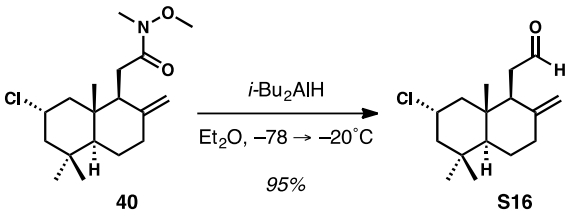
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.63 (s, 1H), 5.21 (s, 1H), 4.54 (s, 1H), 4.02 (m, 1H), 2.53 (ddd, *J* = 19.9, 10.5, 3.12 Hz, 1H), 2.45 (dd, *J* = 16.7, 4.0 Hz, 1H), 2.28 (d, *J* = 10.5, 1H) 1.92 (app. d, *J* = 10, 1H) 1.59–1.56 (m, 1H), 1.55–1.48 (m, 2H), 1.44 (d, *J* = 13.2 Hz, 1H), 1.36 (q, *J* = 12.6 Hz, 1H), 1.25–1.16 (m, 2H), 1.04 (t, *J* = 12.9 Hz, 1H), 0.89 (s, 3H), 0.82 (s, 3H), 0.69 (s, 3H), 0.13 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 203.0, 149.7, 105.9, 73.9, 52.9, 49.2, 41.8, 39.6, 39.2, 38.6, 34.2, 33.4, 29.5, 21.6, 19.2, 14.5, –0.10; **IR** (film) ν 2951, 2845, 2712, 1727, 1649, 1459, 1389, 1250 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{19}H_{34}O_2SiNa$ $[M + Na]^+$: 345.2226; found 345.2229; **$[\alpha]_D^{25}$** -10.4° (*c* = 0.38, $CHCl_3$).



Haterumaimide Q 36. Aldehyde **S15** (9.3 mg, 30 μmol) was subjected to the reaction conditions described for **34** and afforded haterumaimide Q (**36**) as a thin film (5.5 mg, 18 μmol, 52% yield) after flash column chromatography (SiO_2, 60% EtOAc in hexanes). The data obtained for our synthetic sample of **36** matched those reported by Ueda.[39]

For ^{1}H NMR and ^{13}C NMR data comparison to natural **3** in $(CD_3)_3SO$ see Table S19, below.

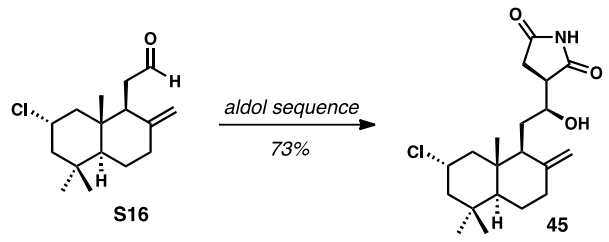
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78, (s, 1H), 5.30 (s, 1H), 4.86 (s, 1H), 4.36 (t, *J* = 7.0 Hz, 1H), 3.99 (dd, *J* = 11.1, 5.4 Hz, 1H), 2.92–2.89 (m, 1H, H_{13}), 2.87 (dd, *J* = 16.5, 5.5 Hz, 1H), 2.67 (dd, *J* = 16.5, 7.6 Hz, 1H), 2.15–2.09 (m, 1H), 1.93 (s, 1H), 1.84–1.76 (m, 1H), 1.59–1.52 (m, 2H), 1.50 (d, *J* = 11.3 Hz, 1H), 1.45 (d, *J* = 13.1 Hz, 1H), 1.17 (td, *J* = 13.1, 4.1 Hz, 1H), 1.14 (td, *J* = 13.1, 2.4 Hz, 1H), 0.95–0.85 (m, 1H), 0.89 (s, 3H), 0.81 (s, 3H), 0.68 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.6, 176.2, 150.8, 104.3, 73.8, 69.1, 53.3, 52.0, 46.8, 41.9, 39.5, 39.1, 33.8, 33.6, 33.5, 29.4, 29.0, 21.6, 19.3, 14.5); IR (film) cm^{-1} ; **HRMS** (ES+) *m/z* calc'd for $C_{20}H_{31}O_4NNa$ $[M + Na]^+$: 372.2151, found 373.2145; **$[\alpha]_D^{25}$** +31.1˚ (*c* = 0.040, $CHCl_3$) [lit.: $[\alpha]_D^{25}$ +36.0˚ (c = 0.19, $CHCl_3$)]



Aldehyde S16.

Alkene **40** (22 mg, 67.2 μmol, 1.0 equiv) was dissolved in Et_2O (1.3 mL, 0.05 M) and the solution was cooled to –78˚C. A solution of *i*Bu_2AlH in toluene (1.0 M, 134 μL, 134 μmol, 2.0 equiv) was added slowly along the side of the flask. After 2 h at –78 ˚C, the flask was warmed to –20 ˚C and quenched with 50 μL of acetone followed by water (200 μL). The biphasic solution was warmed to ambient temperature and diluted with more 1M HCl (1 mL) and water (2 mL). The aqueous phase was extracted with Et_2O (3 x 5 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude oil was purified by chromatography (SiO_2, 5% EtOAc in hexanes) and afforded **S16** a clear oil (17.2 mg, 64 μmol, 95% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.65 (d, *J* = 3.2 Hz, 1H), 4.87 (s, 1H), 4.42 (s, 1H), 4.16 (tt, *J* = 12.6, 3.9 Hz, 1H), 2.54 (ddd, *J* = 17.2, 11.8, 3.3 Hz, 1H), 2.41–2.47 (m, 3H), 2.07–2.13 (m, 2H), 2.00 (ddd, *J* = 12.8, 3.8, 2.2 Hz, 1H), 1.74–1.79 (m, 1H), 1.56 (t, *J* = 12.6 Hz, 1H), 1.45 (t, *J* = 12.2 Hz, 1H), 1.32 (qd, *J* = 12.7, 4.1 Hz, 1H), 1.26 (dd, *J* = 12.6, 2.3 Hz, 1H), 1.24 (s, 3H), 0.88 (s, 3H), 0.76 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 202.4, 147.1, 109.2, 55.4, 54.1, 52.0, 50.5, 49.3, 41.0, 39.6, 37.1, 36.1, 33.3, 23.3, 22.2, 15.1; IR (film) ν 2960, 2853, 2714, 1726, 1345, 1460, 1390, 1339 cm^{-1}; **HRMS** (ES+) *m/z* calc'd for $C_{16}H_{25}OClNH_4$ $[M + NH_4]^+$: 286.1938, found 286.1945; **$[\alpha]_D^{25}$** –1.0° (*c* = 0.52, $CHCl_3$).

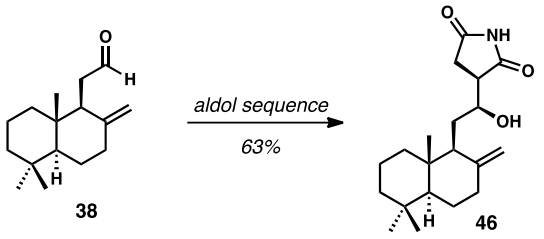


7-Deoxychlorolissoclimide 45.

Aldehyde **S16** (13 mg, 48.4 μmol) was subjected to the reaction conditions described for **34** to yield **45** (13.1 mg, 35.0 μmol, 73% yield) after column chromatography (SiO_2, 55% EtOAc in hexanes) as a clear oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (s, 1H), 4.97 (s, 1H), 4.36 (s, 1H), 4.16 (tt, *J* = 12.2, 3.9 Hz, 1H), 2.89–2.94 (m, 1H), 2.89 (dd, *J* = 17.4, 5.3 Hz, 1H), 2.70 (dd, *J* = 17.3, 8.6 Hz, 1H), 2.45 (ap d, *J* = 13.0 Hz, 1H), 2.23 (d, *J* = 11.4 Hz, 1H), 1.96–2.03 (m, 2H), 1.92 (d, *J* = 3.6 Hz, 1H), 1.72–1.80 (m, 2H), 1.68 (d, *J* = 10.8 Hz, 1H), 1.59 (dd, *J* = 14.0, 7.9 Hz, 1H), 1.52 (t, *J* = 12.8 Hz, 1H), 1.30 (qd, *J* = 15.1, 4.3 Hz, 1H), 1.28 (t, *J* = 11.8 Hz, 1H), 1.13 (dd, *J* = 12.5, 2.5 Hz, 1H), 0.96 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.6, 176.2, 147.7, 108.6, 77.2, 69.3, 55.4, 54.6, 53.6, 52.0, 49.6, 46.8, 42.0, 37.8, 36.1, 33.3, 29.4, 29.2, 23.7, 22.1, 15.0; **IR** (film) ν 3500, 2958, 2936, 2853, 1776, 1712, 1463, 1388, 1186 cm^{-1};

HRMS (ES+) *m/z* calc'd for $C_{20}H_{30}ClNO_3Na$ [M + Na]$^+$: 390.1812, found 390.1820; **[α]$_D^{25}$** +64.3 (*c* = 0.19, $CHCl_3$).



7-Deoxyhaterumaimide Q 46.

Known aldehyde **38** (11.7 mg, 50.0 μmol) was subject to the reaction conditions described for **34** and chromatographically purified (SiO_2, 50% EtOAc in hexanes) to yield **46** (11.0 mg, 33 μmol, 63% yield) as a clear oil. The characterization data were consistent with previously reported data.[40]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 4.91 (s, 1H), 4.67 (s, 1H), 4.35 (ap t, *J* = 6.9 Hz, 1H), 2.93–2.98 (m, 1H), 2.87 (dd, *J* = 17.7, 5.3 Hz, 1H), 2.67 (dd, *J* = 17.7, 9.0 Hz, 1H), 2.42 (ddd, *J* = 12.9, 4.1, 2.5 Hz, 1H), 2.03–1.95 (m, 2H), 1.79–1.66 (m, 3H), 1.65–1.55 (m, 2H), 1.52 (tt, *J* = 13.0, 3.6 Hz, 1H), 1.41 (ap d, *J* = 13.3 Hz, 1H), 1.33 (qd, *J* = 12.9, 4.4 Hz, 1H), 1.17 (td, *J* = 13.4, 3.8 Hz, 1H), 1.08 (dd, *J* = 12.6, 2.7 Hz, 1H), 0.94 (td, *J* = 12.6, 4.2 Hz, 1H), 0.89–0.84 (m, 1H), 0.88 (s, 3H), 0.80 (s, 3H), 0.69 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.9, 176.5, 149.0, 107.4, 69.5, 55.7, 53.8, 46.8, 42.0, 39.8, 39.2, 38.2, 33.6, 33.5, 29.4, 29.1, 24.3, 21.6, 19.3, 14.4; **IR** (film) ν 3441, 3224, 3079, 2933, 2845, 1774, 1713, 1459, 1364, 1188 cm^{-1}; **HRMS** [ES+] *m/z* calc'd for $C_{20}H_{31}O_3NNa$ [M + Na]$^+$: 356.2202, found 356.2203. **[α]$_D^{22}$** +51.1˚ (*c* = 0.35, $CHCl_3$) [lit.: $[\alpha]_D^{20}$ +40.6˚ (c = 0.71, $CHCl_3$)].

3.6.5 Comparison Tables for chlorolissoclimide (1) and haterumaimide Q (2).

Table 3-24. Synthetic and natural chlorolissoclimide (1) in CD_2Cl_2.

Atom	δ C nat. (ppm)	δ C syn. (ppm)	Δ	δ H nat. (ppm)	Multiplicity, *J* (Hz)	δ H syn. (ppm)	Multiplicity, *J* (Hz)	Δ
1	50.1	50.1	-	2.35 1.30	tdd (12.5, 4.0, 2.1) t (12.5)	2.23 1.28	ap d (12.1) t (12.0)	0.12[21] -0.02
2	56.4	56.5	0.1	4.20	tt (12.5, 4.0)	4.20	tt (12.2, 3.9)	-
3	52.8	52.8	-	2.01 1.53	ddd (12.5, 4.0, 2.1) t (12.5)	2.01 1.53	ddd (12.8, 3.9, 2.0) t (12.6)	-
4	36.8	36.7	-0.1	-	-	-	-	-
5	52.9	52.9	-	1.20	s	1.20	s	-
6	34.0	34.0	-	2.10 1.22	s s	2.09 1.22	m s	0.01 -
7	74.1	74.1	-	4.00	d (9.1)	4.00	br s	-
8	150.9	150.9	-	-	-	-	-	-
9	52.3	52.3	-	1.65	dd (11.3, 7.8)	1.63	m (overlapping)	-0.02
10	42.4	42.4	-	-	-	-	-	-
11	29.9	30.0	0.1	1.80 1.60	ddd (14.6, 11.3, 5.6) dt (14.6, 7.8)	1.82 1.60	ddd (15.2, 11.2, 5.6) m (overlapping)	0.02 -
12	69.7	69.7	-	4.32	dddd (7.8, 5.6, 4.0, 2.2)	4.32	m	-
13	47.5	47.5	-	2.90	ddd (9.1, 5.2, 2.2)	2.89	ddd (9.0, 5.1, 2.2)	0.01
14	30.1	30.2	0.1	2.85 2.65	dd (17.7, 5.2) dd (17.7, 9.1)	2.83 2.66	dd (17.8, 5.1) dd (17.8, 9.2)	0.02 0.01
15	180.0	180.3	0.3	-	-	-	-	-
16	177.5	177.8	0.3	-	-	-	-	-
17	105.8	105.9	0.1	5.31 4.92	d (1.6) d (1.6)	5.32 4.91	s s	0.01 -0.01
18	33.8	33.8	-	1.00	s	0.98	s	-0.02
19	22.6	22.7	0.1	0.85	s	0.87	s	0.02
20	15.5	15.6	0.1	0.75	s	0.74	s	-0.01
NH				8.31	br s	8.35	br s	0.04
7-OH				N.O.	-	2.14	d (4.3)	-
12-OH				2.37	br s	2.42	d (2.8)	0.05

Table 3-25. Synthetic and natural haterumaimide Q (3) in $(CD_3)_3SO$

Atom	δ C nat. (ppm)	δ C syn. (ppm)	Δ	δ H nat. (ppm)	Multiplicity, *J* (Hz)	δ H syn. (ppm)	Multiplicity, *J* (Hz)	Δ
1	38.0	38.0	-	1.60 0.91	ddd (13.5, 5.5, 3.0) dd (13.5, 4.0)	1.60 0.91	m td (10.7, 3.7)	- -0.02
2	18.9	18.9	-	1.50 1.42	m m	1.50	m m	-
3	41.5	41.5	-	1.36 1.11	ddd (13.5, 5.5, 3.0) m	1.36 1.53	d (13.0) m	-
4	33.1	33.1	-	-	-	-	-	-
5	52.2	52.2	-	1.12	dd (12.0, 3.5)	1.20	m	-
6	33.5	33.5	-	1.87 1.13	ddd (12.0, 4.4, 3.5) m	1.87 1.22	m m	0.01 -
7	72.0	71.9	- 0.1	3.75	ddd (11.0, 5.5, 4.5)	3.76	dd (9.9, 4.8)	0.01
8	151.1	151.1	-	-	-	-	-	-
9	49.8	49.8	-	1.44	dd (10.0, 5.5)	1.63	dd (12.1)	-0.02
10	38.7	38.6	0.1	-	-	-	-	-
11	29.5	29.5	-	1.58 1.40	m m	1.58	m m	-
12	68.8	66.8	2.0	3.99	dddd (9.0, 6.5, 5.0, 2.0)	3.99	m	-
13	45.3	45.3	-	2.80	ddd (8.5, 5.0, 2.0)	2.80	ap t (6.3 Hz)	-
14	28.9	28.9	-	2.52 2.46	dd (17.5, 5.0) dd (17.5, 8.5)	2.45 – 2.61	m	-
15	181.1	181.1	-	-	-	-		-
16	178.8	178.8	-	-	-	-		-
17	103.6	103.6	-	5.18 4.76	s s	5.19 4.76	s s	0.01 -
18	33.3	33.3	-	0.85	s	0.85	s	-
19	21.5	21.5	-	0.75	s	0.75	s	-
20	14.2	14.2	-	0.57	s	0.58	s	0.01
NH				10.99	br s	10.98	br s	-0.01
7-OH				4.91	d (4.5)	4.89	s	-0.02
12-OH				4.92	d (5.0)	4.90	s	-0.02

3.6.6 Cell Viability Assays

MTS assays were performed for cell viability as described by the supplier (Promega; Madison, WI). Briefly, 5000 cells/well for solid tumor cell lines were seeded in 96-well plates, incubated overnight at 37^{o}C in 5% (v/v) CO_2 and exposed to compounds in a dose-dependent manner for 48 h. For assays using blood tumor cells, 10000 cells/well were seeded in 96-well plates, followed by treating cells with compounds in a dose-dependent manner for 48h. Dimethyl sulfoxide (DMSO) was used as the vehicle control. Viable cells were determined by tetrazolium conversion to its formazan dye. Absorbance was monitored at 490 nm using an automated ELISA plate reader. IC_{50} values were determined using CalcuSyn software.

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4. CHAPTER FOUR

Catalytic C-H Functionalizations Using Amidyl Radicals

4.1 Introduction

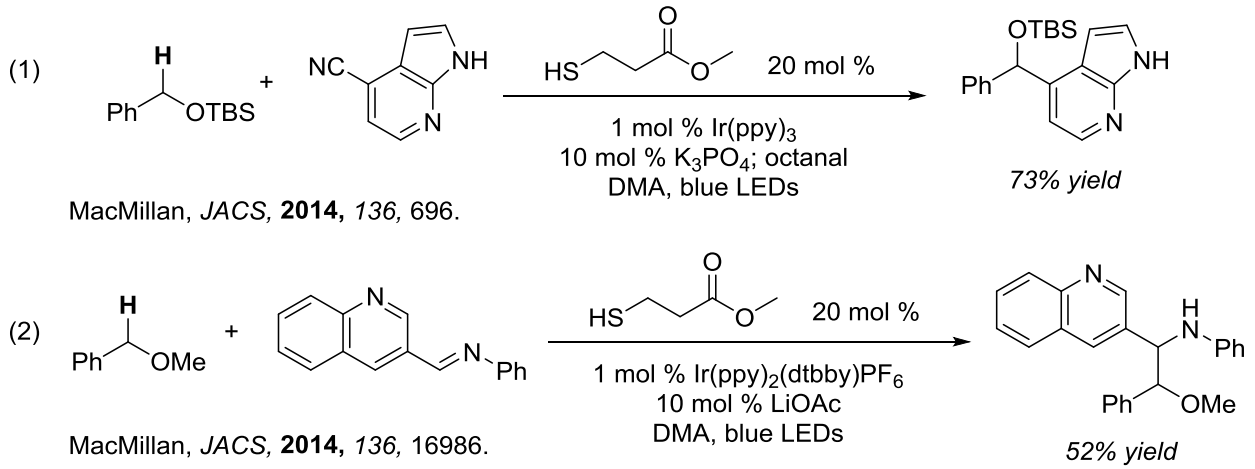
Reactions that can selectively functionalize aliphatic C-H bonds hold significant promise in expediting the synthesis of useful molecules. A wide variety of strategies currently exist toward this goal. These strategies include both stoichiometric and catalytic C-H functionalization reagents. To consider a reaction as a "catalytic C-H functionalization reaction," the species that participates in the C-H abstraction event must be present in substoichiometric quantities. Copper, iron, and manganese complexes have been employed as catalysts to achieve this goal in C-H amination, oxidation and halogenation reactions (see **Chapter 1** for a review of these methods). One of the major benefits of a catalytic C-H functionalization reaction is that of selectivity. Changing the nature of the catalyst or ligand set around the metal center has the potential to alter the selectivity of the reaction – all without throwing away a stoichiometric amount of a complex C-H functionalization reagent. While this paradigm has proven true, only very modest selectivity changes can be seen by modulating the catalyst in existing systems, if at all. Therefore, there exists a need for the development of more modular catalytic C-H functionalization reactions. Systems in which a large number of catalysts can be easily prepared to more deeply study the factors that control selectivity are desperately needed. Reactions of this class offer the potential for asymmetric C-H functionalization, overriding substrate bias, as well as an improved understanding of C-H functionalization methodologies as a whole.

4.2 Background

As discussed above there are a number of protocols that utilize a transition metal complex as the catalyst for a C-H functionalization reaction. These reactions generally rely on an external oxidant such as NaOCl or H_2O_2 to regenerate the catalysts. For reactions of this type developed by White, Groves, Baran, and others see the corresponding section of **Chapter 1.**

Another strategy toward catalytic C-H functionalization, however, involves the use of photoredox catalysis in which the active C-H abstracting agent can be generated via an electron transfer process. David MacMillan, a pioneer in the field of photoredox catalysis has developed a number of different photocatalytic transformations that generate the C-H abstracting agent via this process. An iridium photocatalyst and a base are used to generate a thiol radical via a concerted process called proton coupled electron transfer (PCET). This sulfur centered radical is then able to abstract the benzylic C-H bond on the aryl ether substrates shown in **Figure 4-1.**[1] The subsequently generated carbon centered radical can then participate in arylation reactions or addition to aryl

Figure 4-1. Activation of C-H bonds via photoredox catalysis

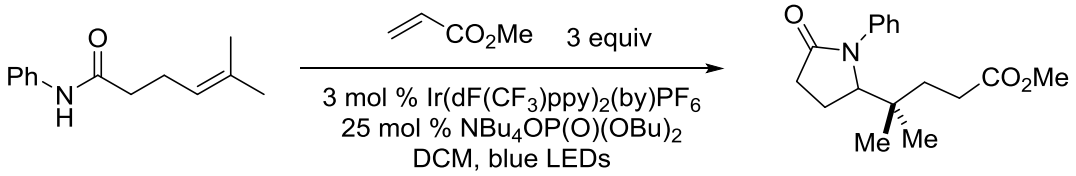


imines. MacMillan has also shown that carbon centered radials can participate in fluorination and

conjugate addition reactions in a photoredox manifold. This offers the potential for a number of different C-H transformations.[2]

It has recently been shown that other heteroatom-centered radicals can be generated through the process of PCET. Knowles and coworkers showed that amidyl radicals can be generated from *N*-phenyl amides and carbamates using a phosphate base and iridium (III) photocatalyts (**Figure 4-2**). The amidyl radical then participates in an intramolecular alkene cyclization and reaction with an olefin acceptor. A number of examples are shown, though only 5-membered rings are formed because the reaction is limited to the kinetically fast *5*-exo radical cyclization.[3] While there is no C-H activation in this particular reaction, the reactivity is promising due to ability of amidyl radicals to participate in C-H abstractions.

Figure 4-2. Alkene carboaminations enabled by proton coupled electron transfer



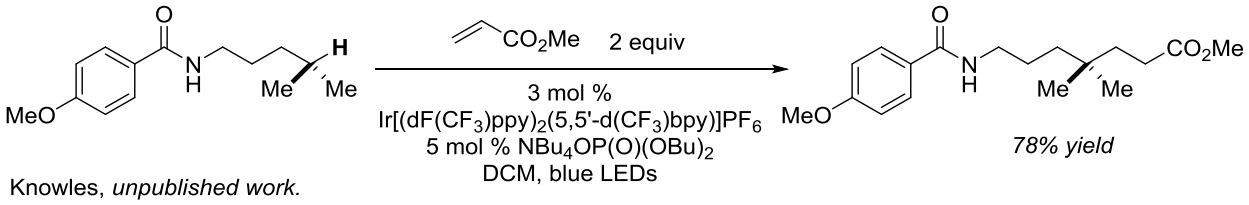
Knowles, *JACS,* **2015,** *137,* 9226.

85% yield

Recently the Knowles group extended the chemistry described above to C-H functionalization applications. By slightly modifying the iridium (III) photocatalyst and switching to a more electron rich amide intramolecular C-H functionalization reactions become possible using this strategy. This photocatalytic Hoffman-Loffler-Freytag reaction benefits from the efficiency of intramolecular 1,5 H-atom abstractions (**Figure 4-3**). For this reason, there are no issues with selectivity, as only a single C-H bond or methylene site will participate in the intramolecular reaction.[4] Although the transformation is an intramolecular reaction the chemistry is powerful; if a similar system could be applied to intermolecular C-H functionalization it would

open the door to C-H fluorination, alkylation, and arylation protocols that are currently inaccessible.

Figure 4-3. Intramolecular C-H functionalization enabled by proton coupled electron transfet



Knowles, *unpublished work.*

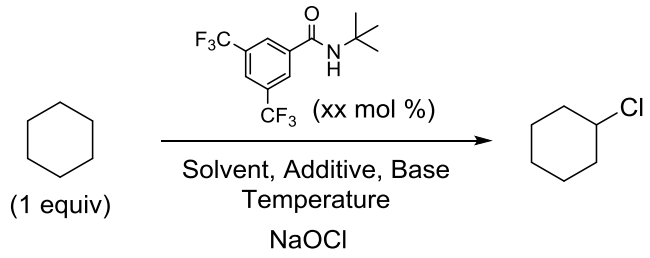
4.3 Reaction Development

We set out to develop an intermolecular aliphatic C-H functionalization reaction based on the reactivity of amidyl radicals we described previously. We began by pursuing two different strategies: (1) identify a stoichiometric halogenating agent compatible with the C-H hlogenation reaction conditions in order to catalytically generate haloamides *in situ*; (2) utilize a photocatalyst to generate an amidy radical directly from an amide via PCET. Initial studies in both areas are outlined below.

4.3.1 Initial Studies – Stoichiometric Halogen Sources

Our approach to developing a catalytic C-H halogenation reaction began first by identifying sources of cationic chlorine or bromine that have been shown to halogenate amides in good yield.[5] These reagents would serve as our stoichiometric halogen sources in the reaction. We first screened conditions using sodium hypochlorite as our stoichiometric source of chlorine, because it is known to generate *N*-Chloroamides in good yields and short reaction times.[6] Sodium hypochlorite was added to the optimized C-H chlorination conditions with benzoyl peroxide radical initiator (**Table 4-1**, entry 1). No product was observed, however, switching to ethyl acetate

Table 4-1. Efforts toward catalytic C-H chlorination with NaOCl



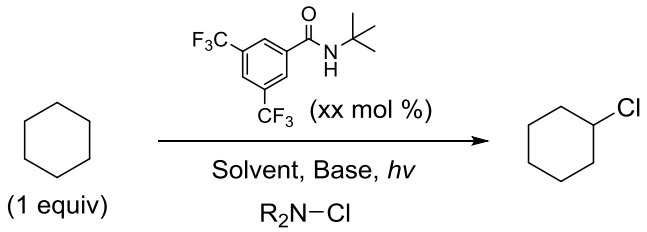
Entry	Solvent	Amide	Temp	Base	Additive	Initiator	Result
1	PhH	20%	65	none	none	BPO	NR
2	EtOAc	20%	65	none	none	BPO	35% yield
3	EtOAc	none	65	none	none	BPO	36% yield
4	PhH	20%	65	none	t-BuOH	*hv*	38% yield
5	DCM	20%	65	none	t-BuOH	*hv*	37% yield
5	DCM	20%	65	Cs_2CO_3	t-BuOH	*hv*	NR
6	DCM	none	65	none	t-BuOH	*hv*	16% yield

a) Yield based on alkane, determined by GC analysis

as the solvent resulted in a 35% yield of chlorocyclohexane product. Control experiments showed an equivalent background reaction in the absence of amide (**Table 4-1**, entries 2 and 3). We attribute the background reaction to C-H abstraction by benzoyl radicals formed from the benzoyl peroxide (BPO) initiator, resulting in a switch from radical to light initiation. We found that we were able to obtain similar yields using visible light initiation and sub-stoichiometric tBuOH (**Table 4-1**, entries 4 and 5). This generates tBuOCl *in situ*, which is a more active chlorinating agent, known to efficiently chlorinate nitrogen containing molecules.[7] Control experiments revealed that the addition of catalytic amide improves the reaction efficiency, though there is still a significant background reaction (**Table 4-1**, entry 6). This data, however, suggests the formation of *N*-chloroamide during the course of the reaction.

Based on the significant background reaction observed using hypohalite chlorine sources, we screened a number of electrophilic chlorine sources. All of the sources screened contain N-Cl bonds. The N-Cl bond of *N*-chloroimines, for example, is not homolyzed using visible light. Therefore we hypothesized chlorine transfer might occur to our amide preferentially to generate our desired *N*-chloroamide *in situ*. To this end, trichlorisocyanuric acid (TCIA), dichlorohydaontoin, and *N*-chlorophthalimide all gave the desired chloroalkane product in a range of yields, while *N*-Chlorosuccinimide and chloramine-T resulted in no reaction (**Table 4-2**). We were particularly pleased with chlorination results with TCIA in DCM (**Table 4-2,** entry 1), though

Table 4-2. Efforts toward catalytic C-H chlorination with other N-Chloro reagents

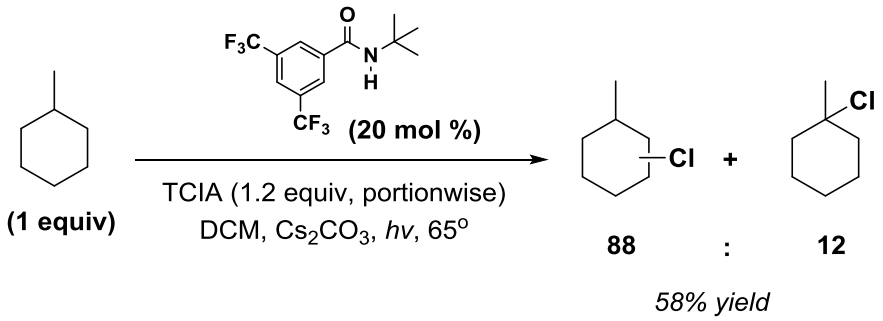


Entry	Solvent	Amide	Chlorine Source	Temp	Base	Result
1	DCM	20%	TCIA	65	Cs_2CO_3	68% yield
2	DCM	20%	TCIA	40	Cs_2CO_3	50% yield
3	CCl_4	20%	TCIA	65	Cs_2CO_3	37% yield
4	DCM	none	TCIA	65	Cs_2CO_3	15% yield
5	DCM	20%	dichlorohydantoin	65	Cs_2CO_3	37% yield
6	DCM	none	dichlorohydantoin	65	Cs_2CO_3	33% yield
7	DCM	20%	NCS	65	Cs_2CO_3	NR
8	PhH	20%	NCS	65	Cs_2CO_3	NR
9	DCM	20%	N-Cl Phthalimide	65	Cs_2CO_3	10% yield
10	PhH	20%	N-Cl Phthalimide	65	Cs_2CO_3	6.0% yield
11	PhH/H_2O	20%	Chloramine-T	65	Cs_2CO_3	NR

a) Yield based on alkane, determined by GC analysis

we also observed a significant background reaction without amide (**Table 4-2**). In order to probe the active C-H abstracting species in the reaction we repeated the conditions for **Table 4-2**, entry 1 using methyl cyclohexane as the substrate and measured the percentage of tertiary alkyl halide product formed in the reaction. We observed a 12:88 ratio of tertiary to secondary alkyl chloride products in the reaction in a combined 58% yield (**Figure 4-4**). The presence of inorganic base in the reaction should suppress any undesired chlorine radical reactivity, this suggests that the erosion of selectivity compared to C-H chlorination with stoichiometric *N*-chloroamide (see **Chapter 3**) arises from some other source. We hypothesize that once a carbon centered radical is formed in the reaction, chlorination of that radical can be accomplished via *N*-chloroamide or TCIA. Chlorination with TCIA would result in formation of an imidyl radical that erodes the selectivity of the reaction.

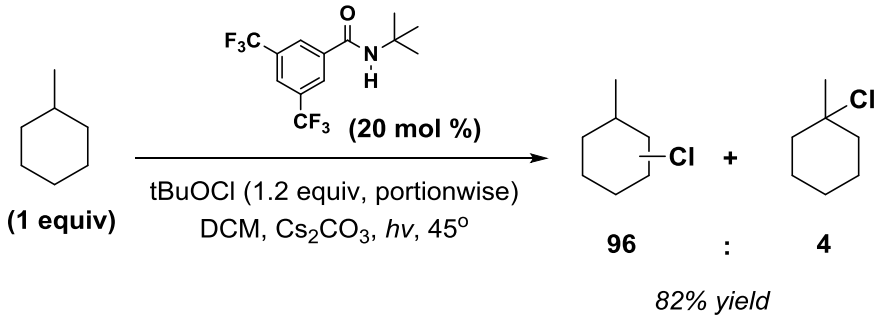
Figure 4-4. Catalytic chlorination using trichlorisocyanuric acid (TCIA)



Lastly, we pursued the strategy of portion wise addition of a stoichiometric chlorine source. Neat tBuOCl was the obvious choice because *N*-chlorination with this reagent occurs on a rapid timescale. We subjected methylcyclohexane to chlorination with 20 mol % of amide and 1.2 equivalents of tBuOCl. The oxidant was added in 6 portions of 20 mol %. We were pleased to see that this approach preserved the selectivity of our previously developed C-H chlorination

reaction, while increasing the efficiency of the reaction by roughly 10% (**Figure 4-5**). The portion wise addition strategy limits undesired the background C-H chlorination by tBuOCl.

Figure 4-5. Catalytic C-H chlorination using *t*-BuOCl

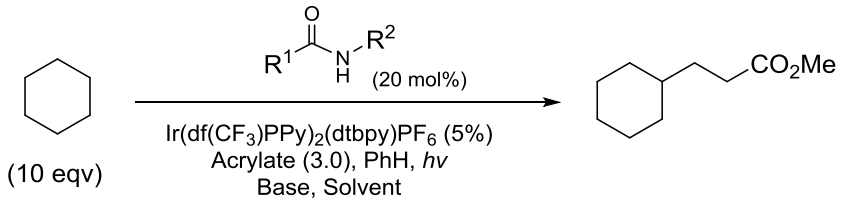


4.3.2 Initial Studies – Photoredox Manifolds

Our second major approach toward developing a catalytic intermolecular C-H functionalization with amidyl radicals involves a photoredox manifold. Our initial work in this area is inspired by the chemistry developed by MacMillan and Knowles discussed above (**Section 4.2**). We began by pursuing a photocatalytic conjugate addition reaction with the goal of directly transforming C-H bonds into C-C bonds. We envisioned that in the presence of base ad photocatalyst an amidyl radical would be generated from the parent amide. Subsequent C-H abstraction would yield a carbon centered radical that could then participate in a radical addition to an alkene to form a carbon-carbon bond. Initial studies by the Knowles group (described above) provide precedent for each mechanistic step required for the reaction to proceed.

We began by choosing a strongly oxidizing iridium (III) complex used successfully in multiple photoredox mainfolds. We screened a number of different bases and amides against the catalyst to evaluate which combination would give the highest yield of desired product (**Table 4-3**). The amide used in our previous studies and tetrabutylammonium phosphate base gave a small, but measurable amount of product in the reaction (**Table 4-3,** entry 1). Switching to *N*-

Table 4-3. Amide and base screen for photocatlytic conjugate addition reaction



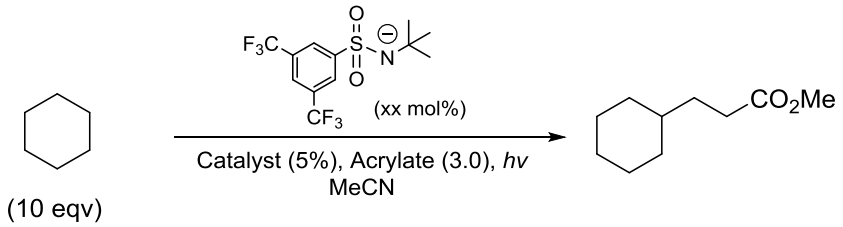
Entry	Solvent	Amide	Base	Result
1	PhH	R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu	$NBu_4OP(O)(OBu)_2$	2% yield
2	PhH	R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = 3,5-$(CF_3)_2C_6H_3$	$NBu_4OP(O)(OBu)_2$	4% yield
3	PhH	R^1 = Ph; R^2 = 4-BrC_6H_4	$NBu_4OP(O)(OBu)_2$	4% yield
4	PhH	R^1 = Ph; R^2 = Ph	$NBu_4OP(O)(OBu)_2$	2% yield
5	PhH	R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu (Sulfonamide)	$NBu_4OP(O)(OBu)_2$	5% yield
6	MeCN	R^1 = 3,5-$(CF_3)_2C_6H_3$; R^2 = *t*Bu (Sulfonamide)	$NBu_4OP(O)(OBu)_2$	8% yield
7	PhH	none	$NBu_4OP(O)(OBu)_2$	8% yield
8	PhH	none	Cs_2CO_3	NR
9	PhH	none	$NaOP(O)(OBu)_2$	NR
10	PhH	none	NBu_4OBz	3% yield
11	PhH	none	none	NR

a) Yield based on amide, determined by GC analysis

phenyl amides (**Table 4-3,** entries 2, 3 and 4) due to their ability to participate in PCET unfortunately yielded similar results. We postulated that amides with a more acidic N-H bond might give more favorable results. Therefore we probed the ability of sulfonamides to participate in the reaction (**Table 4-3,** entries 5 and 6). While the substitution of amide for sulfonamide gave a slight boost in yield, the background reaction (**Table 4-3,** entry 7) gave nearly identical results. In order to identify the source of the background reaction we conducted a number of control experiments. Our control experiments point to the involvement of the tetrabutylammonium cation

as the source of background reactivity. In order to eliminate potential false positives from the base in the reaction, we chose to pursue a strategy in which base in not a necessary reaction component.

Table 4-4. Catalyst screen for photocatalytic conjugate addition



Entry	Sulfonamide Salt	Catalyst	Result
1	20 mol %	$Ir(df(CF_3)PPy)_2(dtbpy)PF_6$	15 % yield
2	none	$Ir(df(CF_3)PPy)_2(dtbpy)PF_6$	NR
3	20 mol %	$Ir(ppy)2(dtbby)PF_6$	3 % yield
4	20 mol %	$Ir(ppy)_3$	NR
5	20 mol %	$Ru(Bpz)_3$	NR
6	20 mol %	10-Me-9-Mes Acridinium	NR
7	100 mol %	$Ir(df(CF_3)PPy)_2(dtbpy)PF_6$	6% yield

a) Yield based on amide, determined by GC analysis

To circumvent the need for base in the reaction we first generated a salt by deprotonating our sulfonamide with sodium hydride. We found the salt to be soluble in acetonitrile, and chose to screen the salt against a number of photocatalysts. We were pleased to see an increase in reaction efficiency by applying this strategy (**Table 4-4,** entry 1). We determined the oxidation potential of the sulfonamide salt (0.95eV) using cyclic voltammetry experiments. A number of other catalysts that are capable of oxidizing this salt were examined in the reaction, though none gave improved reaction yields. We attribute the lack of reaction in the case of the $Ru(Bpz)_3$ and 10-Me-9-Mes acridinium photocatalysts to nucleophilic attack by the sulfonamide salt. Additionally, decreased yields corresponding to an increased amount of sulfonamide in the reaction suggests the potential

for catalyst degradation by amidyl radicals. We hypothesize, therefore, additional catalyst should be screened in order to uncover an optimal system for this reaction.

4.4 Summary

We have begun to develop two major strategies for developing catalytic C-H functionalization reactions. The first involves identifying a stoichiometric halogenating agent that generates *N*-haloamides *in situ*. We have achieved success with this strategy by using portion wise addition of tBuOCl. The second strategy involves the use of a photocatalyst to generate the amidyl radical through an electron-transfer process. Our initial results in this area are promising – initial studies show a C-H conjugate addition reaction will be possible. In order to improve on our initial results a wider variety of photocatalysts, amides, bases, and alkene acceptors will need to be thoroughly screened. In addition we hope to use this photoredox manifold to affect other C-H transformations including fluorination and arylation reactions.

4.5 Experimental Data

Test reactions are set up in the glovebox in degasses solvents and run according to procedures laid out in **Chapter 2 and 3.** All materials used are commercially available or prepared via literature procedures. The reactions are analyzed for yield and selectivity using GC. The light source for the photoredox reactions are 450nm 34 W Kessil LED bulbs.

4.5.1 Sample Procedure for Catalytic Chlorination (Figure 4-5)

To a flame-dried vial with PTFE cap 150mg of amide (0.48 mmol, 20 mol %) was added followed by cesium carbonate (156 mg, 0.48 mmol, 20 mol %) and methyl cyclohexane (293 uL, 2.39 mmol, 1.0 equiv). The reaction was dissolved in 400 uL of DCM. 5 portions of tertbutyl hypochlorite (50 uL, 20 mol % each) were added in 4 hour increments. After each addition of tert

butyl hypochlorite the reaction was stirred in the dark for 1 hour, followed by visible light irradiation at 45^{o}C for 4 hours. Direct analysis of the crude reaction mixture by GC revealed 82% combined yield of alkyl chloride products. 4% of the product balance consisted of 1,1-chloromethylcyclohexane, while the remainder of the product mixture consisted of secondary alkyl chloride products.

4.5.2 Sample Procedure for Photocatalytic Conjugate Addition (Table 4-4, Entry 8).

To a flame-dried vial with PTFE cap, 16 mg of sulfonamide salt (0.44 mmol, 20 mol %) was added, followed by 200 uL cyclohexane (1.76 mmol, 10.0 equiv) 21 uL acrylate (0.24 mmol, 1.0 equiv) and 5 mg of Ir (III) catalyst (0.0044 mmol, 2 mol %). The reaction was dissolved in 1 mL of $PhCF_3$. The vial was then sealed and placed between two 34W blue Kessil LED lamps and irradiated overnight. The internal temperature of the reaction reached 40^{O}C, and the color of the reaction changed from yellow to black. GC analysis of the crude reaction mixture revealed a 33% yield of desired product with respect to amide in the reaction.

4.6 REFERENCES

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(2) (a) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2014,** *136,* 10886; (b) Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. *J. Am. Chem. Soc.,* **2015,** *137,* 5654;

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(5) (a) Bew, S. P.; Hughes; Palmer, N. J.; Savic, V.; Soapi, K. M.; Wilson, M. A. *Chem. Commun.*, **2006** , *41,* 4338 (b) Timberlake, J. W.; Alender, J.; Garner, A. W.; Hodges, M. L.; Oezmeral, *J. Org. Chem.*, **1981** , *46,* 2082 (c) Neale, R.S. *J. Am. Chem. Soc*., **1966** , *88,* 3051 (d) Makosza, M.; Bobryk, K.; Krajewski, D. *Heterocycles*, **2008** , *76,* 1511.

(6) (a) Quinn, R. K.; Könst, Z. A.; Michalak, S. A.; Schmidt, Y.; Szklarski, A. R.; Flores, A. R.; Nam, S.; Horne, D. A.; Vanderwal, C. D.; Alexanian, E. J.; *J. Am. Chem. Soc.*, **2016**, *138*, 696 (b) (a) Zhong, Y.-L.; Zhou, H.; Gauthier, D. R.; Lee, J.; Askin, D.; Dolling, U. H.; Volante, R. P. *Tetrahedron Lett.*, **2005**, *46*, 1099; (c) Zhong, Y.-L.; Bulger, P. G. *Org. Syn*. **2010**, *87*, 8.

(7) Xuan, M.; Paterson, I.; Dalby, S. M. *Org. Lett.*, **2012** , *14*, 5492

5. CHAPTER FIVE

Alkene Carbooxygenations Using Hydroxamic Acids

5.1 Introduction

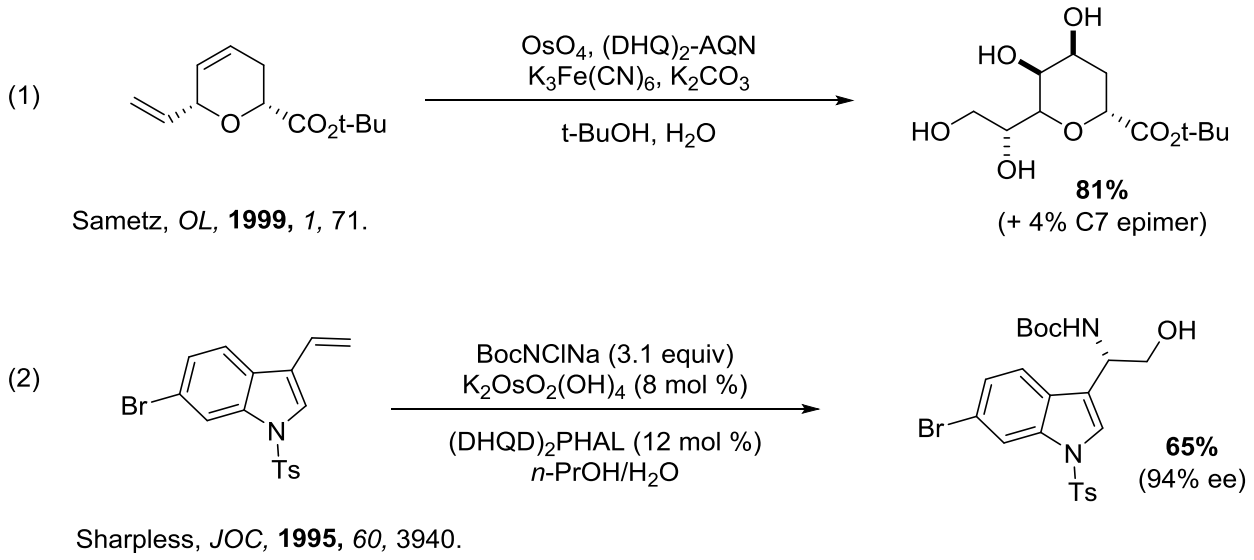
Alkenes are an abundant and versatile functional group for chemical synthesis. Simple alkene starting materials are among the most widely available, naturally abundant, and diverse classes of starting materials for use in complex synthesis. The abundance of alkene starting materials exists for two main reasons: (1) they are easily derived from petrochemical feedstocks, and (2) alkenes can be selectively prepared from a wide variety of organic starting materials. Additionally, alkenes themselves are useful chemical building blocks because they participate in a diverse set of chemical transformations including polar, radical, pericyclic, and organometallic pathways. Carbon-carbon unsaturation is a robust synthetic handle, often unaffected by many harsh reaction conditions. Synthetic methods that introduce useful functionality from readily available starting materials are extremely important to the development of new efficient pathways to materials, pharmaceuticals, and agrochemicals.

The ability to create densely functionalized, stereochemically defined molecules from simple, easily accessed, starting materials is central to developing bioactive small molecules that have the potential to improve human health. Alkene difunctionalization, the addition of two functional groups across a carbon-carbon double bond, has emerged as one of the leading methods for the stereoselective introduction of heteroatomic functionality in synthesis. This added

functionality may be necessary in the final product or further elaborated in subsequent manipulations.

In the 1970s osmium-catalyzed alkene difunctionalizations emerged as the premier reaction class for asymmetric installation of 1,2 diols and 1,2 aminoalcohols.[1] Asymmetric osmium alkene difunctionalizations were developed by Prof. Sharpless. The origin of selectivity in the reactions rely on the use of dihyroquinnone ligands – controlling wethere the herteroatom functionality is delivered from the top or bottom face of the alkene.[2] The methodologies developed by Sharpless have been widely used in synthesis (**Figure 5-1**) for the installation of cis diols and amino alcohols.[3] Recent advances, however, have moved away from Os in favor of palladium-catalyzed variants and some metal-free processes.

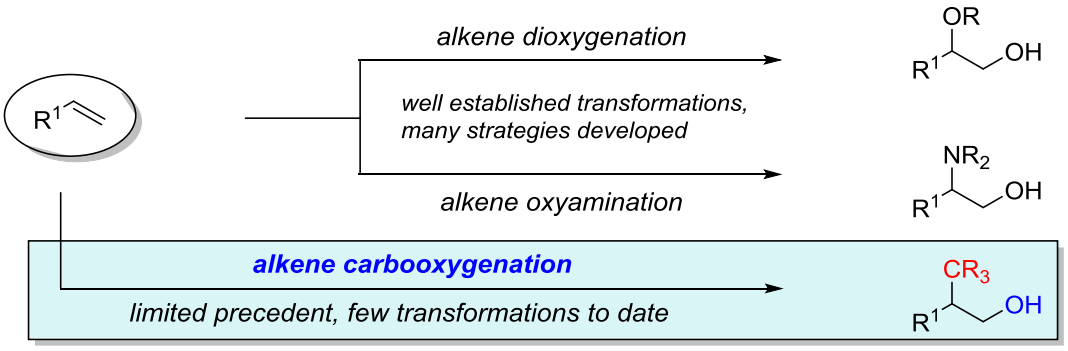
Figure 5-1. Osmium alkene dufunctionalizations



5.2 Background

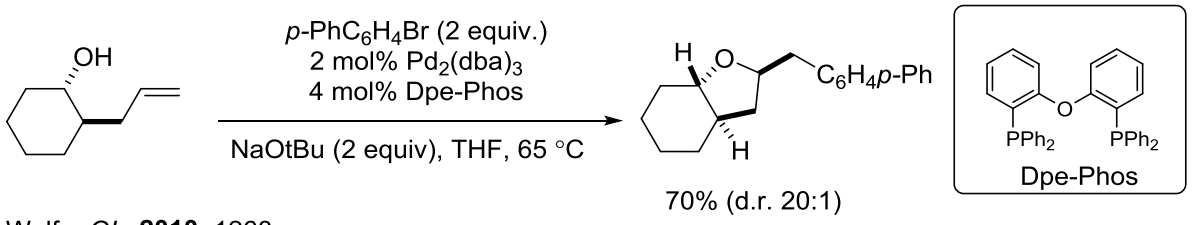
In the past two decades, a plethora of alkene oxyamination[4] and dioxygenation[5] methods have emerged. Other modes of difunctionalization, however, are still scarce (**Figure 5-2**). Carbooxygenations in particular, reactions that form both a C-C and C-O bond, are significantly underdeveloped. Our studies aim to develop carbooxygenation reactions using a radical-mediated process to further expand the scope of alkene difunctionalizations.

Figure 5-2. Alkene difuctionalization types



Reactions that accomplish the addition of carbon and oxygen across an alkene in a single step were virtually unknown until this past decade. During this time, two main strategies have surfaced to tackle this synthetic problem. The first approach makes use of transition metal catalysis.[6] For example, Wolfe and coworkers disclosed the palladium-catalyzed carboetherification of alkenes with aryl bromides shown in (**Figure 5-3**).[6a] Although this protocol realizes a challenging transformation, it is limited to delivering a confined set of oxygen- and carbon-based functionality, namely that the carbon-containing component is an arene.

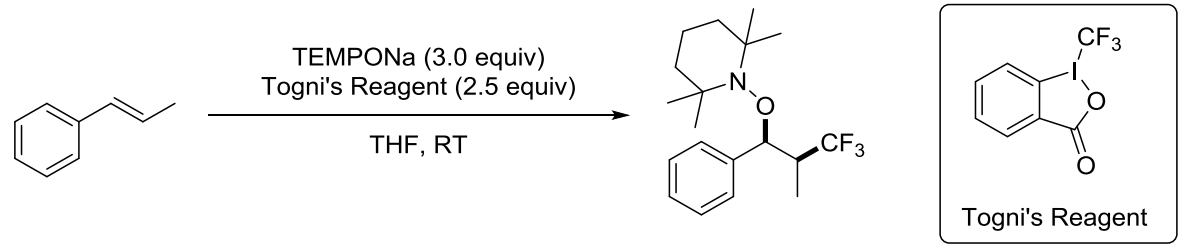
Figure 5-3. Palladium-catalyzed carboetherification



Wolfe, *OL,* **2010,** 1268.

Radical mediated approaches have also been successfully developed to achieve carbooxygenation.[7] These transformations feature the addition of nucleophilic carbon-centered radicals to alkenes followed by radical trapping with a persistent oxygen-centered radical (i.e. TEMPO). Just last year, the Studer group utilized this tactic to affect the net oxytrifluoromethylation of alkenes using Togni's reagent (equation 2).[7c] Despite the utility of these radical carbooxygenation pathways, they are inherently limited to transformations that involve rapid carbon-centered radical additions to alkenes. Additionally, the oxygen-containing component must come from a persistent radical species.

Figure 5-4. Radical-based carbooxygenation using persistent radical TEMPO



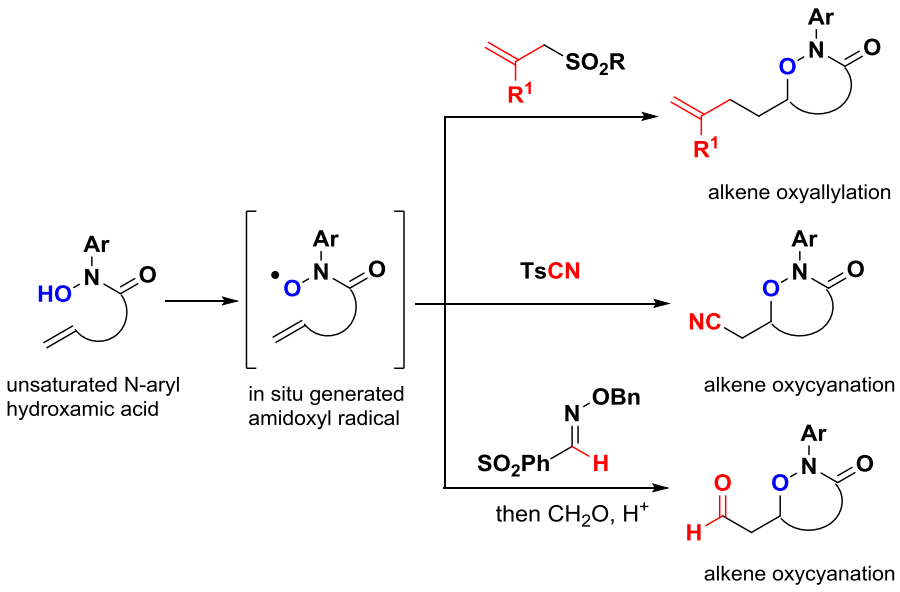
Studer, *ACIE,* **2012,** 8221,

5.3 Reaction Development

We postulated that a complementary radical-mediated approach to alkene carbooxygenation could proceed by the initial addition of an oxygen-centered radical to an alkene followed by subsequent carbon-carbon bond formation. Such a strategy, which introduces the carbon-atom

functionality in the second bond-forming step, capitalizes on the wealth of well-established radical-mediated methods available to form carbon-carbon bonds. This would enable a variety of unique transformations of alkenes. We have previously demonstrated the utility of in situ generated amidoxyl radicals to facilitate radical-mediated dioxygenations and oxyaminations of alkenes.[8] We envisioned that following the cyclization of the amidoxyl radical, subsequent reaction with an allyl sulfone, tosyl cyanide, or a sulfonyl oxime ether would enable direct alkene oxyallylation, oxycyanation, and oxyacylation respectively (**Figure 5-5**).

Figure 5-5. Carbooxygenation strategy



5.3.1 Initial Studies

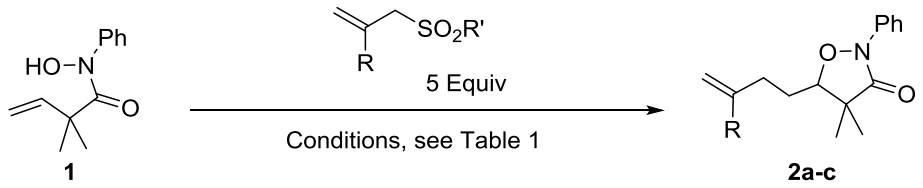
Our oxyallylation studies commenced with *N*-aryl hydroxamic acid **1** as a test substrate and ethyl allyl sulfone as a radical trap. We initially surveyed a variety of non-polar and polar solvents suitable for radical reactions, including those used in our previous alkene difunctionalization studies (Table 1, entries 1-4). The reaction of substrate **1** in the presence of ethyl allyl sulfone (5 equiv) at 60 ˚C in PhCN delivered allylated isoxazolidinone **2**, albeit in low

yield (**Table 5-1**, entry 1). Increasing the temperature and switching to more polar solvents resulted in a modest increase in both reaction rate and yield (**Table 5-1**, entries 4 and 5). In these initial experiments, conversions were moderate even with prolonged reaction times, decreasing overall efficiency. In order to address this issue, we attempted an oxyallylation in the presence of AIBN, a radical initiator. Radical initiators have proven useful in increasing reaction rates in other alkene difunctionalizations using hydroxamic acids.[9] In this case, while increased rates were observed upon the addition of AIBN, numerous byproducts were formed and there was no increase in yield of the desired product. Additionally, the role of the sulfonyl leaving group was studied (**Table 5-1**, entries 5-7). Changing this group, however, yielded only similar or decreased reaction efficiencies.

With limited success in our initial studies, we became intrigued by the possibility of a hydrogen-bond donor facilitating the oxyallylation process. We speculated that such a reagent could increase the efficiency of the reaction by two potential pathways: increasing the reactivity of the amidoxyl radical, or influencing the conformation of the substrate to favor reactivity. Recently, Lewis acids have been shown to greatly increase the reactivity of nitroxide radicals (e.g. TEMPO),[10] supporting the possibility of generating a more reactive amidoxyl radical through hydrogen bonding. In addition, hydroxamic acids are known to form inter- and intramolecular hydrogen bonds, which could serve to lower rates of reaction. While the specific mode of activation remains to be identified, the addition of 50 mol % of $PhSO_2NH_2$ afforded significan increases in both reaction rate and efficiency (**Table 5-1**, entry 6). Substituting ethyl allyl sulfone for more electron-poor allylating agents further increased yields (**Table 5-1**, entries 7-9). The oxyallylation of substrate **1** with the 2-SO_2Ph-substituted allyl sulfone (**Table 5-1**, entry 9) proceeds in a remarkable 95% isolated yield, and is in fact more efficient than either the previously reported dioxygenation or

oxyamination of that substrate.[8a,b] While these reactions do require an excess of allylating agent due to the slow reaction rates, recovery of the unreacted sulfone is trivial.

Table 5-1. Optimization of intramolecular alkene oxyallylation[a]



1 **2a-c**

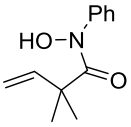
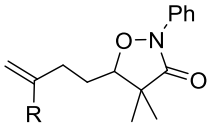
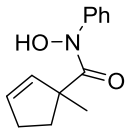
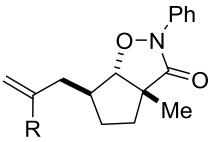
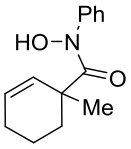
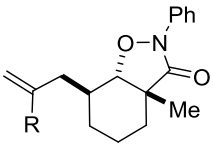
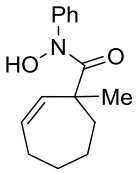
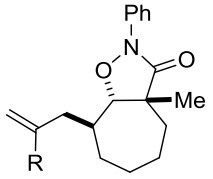
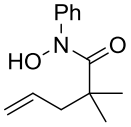
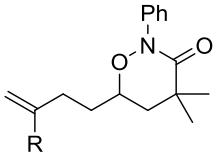
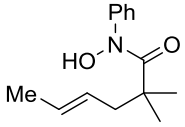
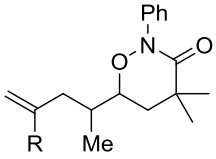
Entry	R, R'	Additive	Solvent	[°C]/ [h]	Yield [%]
1	H, Et	none	PhCN	60/50	15
2	H, Et	none	PhCN	80/36	26
3	H, Et	none	AcOH	80/24	20
4	H, Et	none	DMSO	80/48	37
5	H, Ph	none	DMSO	80/48	35
6	H, Allyl	none	DMSO	80/18	26
7	H, CF_3	none	DMSO	80/5	13
8	H, Et	AIBN[a]	DMSO	80/24	34
9	H, Et	$PhSO_2NH_2$[b]	DMSO	85/36	53
10	CO_2Et, Et	$PhSO_2NH_2$[b]	DMSO	85/36	56
11	**SO_2Ph, Ph**	**$PhSO_2NH_2$[b]**	**DMSO**	**85/36**	**95**
12	SO_2Ph, Ph	none	DMSO	85/48	77

[a] Add 10 mol % added every hour until completion. [b] 50 mol % added

5.3.2 Substrate Scope – Oxyallylation Reactions

Upon identifying a suitable protocol for oxyallylation, we next investigated the substrate scope using a variety of hydroxamic acid substrates (**Table 5-2**). Oxyallylations involving 5-*exo* cyclizations proceeded in moderate to high yield with both cyclic and acyclic substrates, with reaction efficiencies consistently higher with electron-poor allyl sulfones (**Table 5-2**, entries 1-4). The oxyallylation of cyclopentenyl-, cyclohexenyl-, and cycloheptenyl substituted hydroxamic acids all delivered bicyclic isoxazolidinone products in moderate to good yields (**Table 5-2**, entries 2-4). While the difunctionalization of cyclopentenyl substrate **3** proceeded with good

Table 5-2. Alkene oxyallalation substrate scope[a]

Entry	Substrate	Product	yield [a],[b],[c],
1	 **1**		**2a** 53% (R=H) **2b** 56% (R=CO_2Et) **2c** 98% (R=SO_2Ph)[f]
2	 **3**		**4a** 30% (R=H) (91:9 dr) **4b** 55% (R=CO_2Et) (90:10 dr) **4c** 65% (R=SO_2Ph)[d] (90:10 dr)
3	 **5**		**6b** 69% (R=CO_2Et) (58:42 dr) **6c** 84% (R=SO_2Ph)[f] (52:48 dr)
4	 **7**		**8b** 63% (R=CO_2Et) (69:31 dr) **8c** 86% (R=SO_2Ph)[f] (72:127 dr)
5	 **9**		**10** 37% (R=SO_2Ph)[d] (82%)[e]
6	 **11**		**12** 41% (R=SO_2Ph)[d] (50:50 dr)

[a]All reactions run 0.5M in DMSO with 5 equiv. Allyl Sulfone at 85 °C. [b]Yields of isolated product. [c]Diastereomeric ratio based on crude NMR [d]NMR yield. [e]Yield based on recovered starting material. [f]3.5 Equiv Sulfone added.

diastereoselectivity to provide the *trans* oxyallylation product **4**, reactions of substrates **5** and **7** proved relatively unselective. The reactions of acyclic substrates **9** and **11** demonstrate that oxyallylation involving 6-exo cyclizations are also viable, albeit in moderate yield (**Table 5-2**, entries 5-6). The decreased efficiencies of these reactions are due to the relatively low conversions

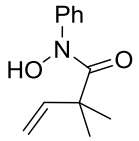
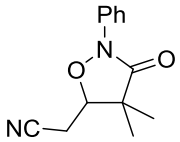
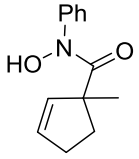
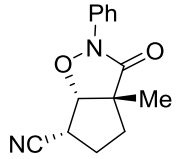
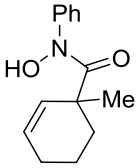
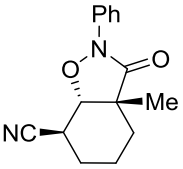
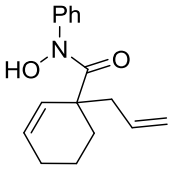
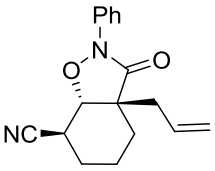
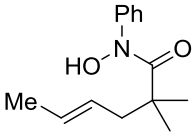
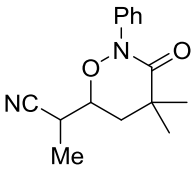
of substrate involving the slower 6-*exo* cyclization step—the oxyallylation of substrate **9** delivers [1,2]-oxazinone **10** in good yield based on recovered starting material. All attempts to further increase reaction conversion in these cases with the use of radical initiators (or single electron oxidants) were unsuccessful.

5.3.3 Substrate Scope- Oxycyanation and Oxyacylation Reactions

Substituting tosyl cyanide (TsCN) for the allyl sulfone reagent under slightly modified conditions leads to a radical-mediated alkene oxycyanation protocol that proceeds with similar efficiencies (Table 3). For example, the reaction of substrate **1** with TsCN (3 equiv) in EtCN at 60 ˚C in the presence of 10 mol % DLP (dilauroyl peroxide) provided oxycyanation product **2d** in 61% isolated yield (Table 3, entry 1). The diastereoselectivity of the oxycyanation process was similar to that of the oxyallylation process, as reactions of cyclohexenyl substrates **5** and **15** both favored *trans* difunctionalization to a small degree. Notably, substrate **15** undergoes mono-difunctionalization under these conditions (Table 3, entry 3). A similar selectivity would not be likely using most existing carbooxygenation methods. For example, both alkenes in substrate **15** would undergo difunctionalization if subjected to the radical manifold described by Studer and coworkers. The oxycyanation of substrate **11** delivers cyanosubstituted [1,2]-oxazinone **17** in moderate yield, demonstrating the ability of the oxycyanation to proceed via 6-*exo* ring-closure. Substrate **3,** however, delivered the *cis* isomer of the product in moderate yield and good selectivity.

This selectivity observed in the formation of **4d** is opposite the selectivity seen in all of the other bicyclic carbooxygenation products synthesized, as well as deoxygenation and oxyamination products synthesized earlier. Our working hypothesis for this observation is that the *trans* isomer

Table 5-3. Alkene oxycyanation substrate scope[a]

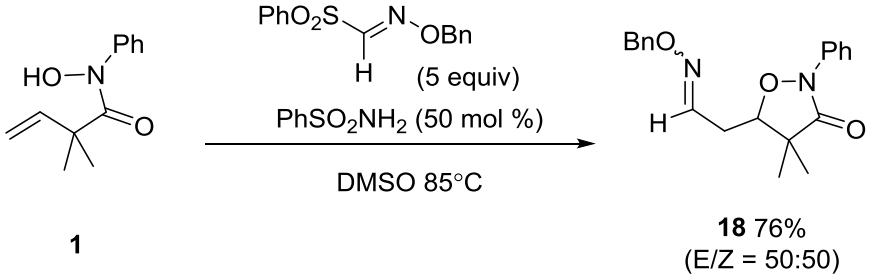
Entry	Substrate	Product	yield[a],[c],[d]
1	 **1**		**2d** 61%
2	 **3**		**4d** 34% (>95:5 dr)
3	 **5**		**6d** 57% (62:38 dr)
4	 **15**		**16** 52% (68:32 dr)
5	 **11**		**17** 41% (50:50 dr)

[a]All reactions run 0.5M in EtCN with 2 equiv. TsCN at 60 °C. [b]Yields of isolated product. [c]Diastereomeric ratio based on crude NMR

is actually formed during the reaction but somehow degraded by an unproductive radical pathway, leaving the minor product in low yield and seemingly good selectivity. Further experiments to elucidate the source of this paradox are ongoing.

A third carbooxygenation variant that we targeted during these studies was a radical-mediated alkene oxyacylation. We viewed this transformation as particularly attractive due to the versatility of the aldehyde product for post reaction modidificcation, as well as the construction of the valuable b-alkoxy aldehyde motif. Our approach to this process was inspired by the innovative work of Kim and Lim,[11] who demonstrated the utility of phenylsulfonyl oximes to deliver formal acylation products.We envisioned that further hydrolysis of the initial oxime products would deliver the desired aldehydes.[12] Under identical conditions to the oxyallylation reactions phenyl sulfonyl benzyl oxime ether reacted with substrate **1** to afford the oxime product in good yield, in a 50:50 E to Z ratio about the C-N double bond (see equation 3). Deprotection of the oxime ether proved to be trivial (>90%). The aldehyde product can be revealed by subjecting oxime ether **18** to a mixture camphor sulfonic acid (CSA) and aqueous formaldehyde at room temperature. With an initial oxyacylation result in hand, the substrate scope of the reaction was studied briefly to see if it was congruent with our earlier findings. The findings for alkene oxyacylation are consistent

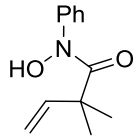
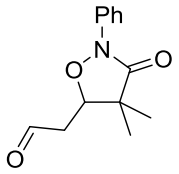
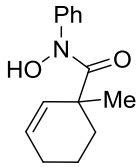
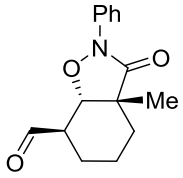
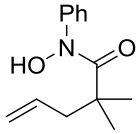
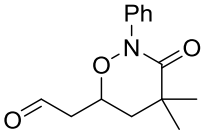
Figure 5-6. Initial oxime formation in oxycyanation reaction



with those seen the other carbooxygenations described above in terms of efficiency and selectivity. The variant proceeds in good to moderate yields over the two steps for substrates that undergo the 5-*exo* radical ring closure. Additionally, in the case of cyclic substrate **5**, the bicyclic products showed a slight preference for the *trans* diastereomer. The reaction of substrate **11** illustrates the

capability of the oxyacylation to procede via a 6-*exo* radical cyclization as well as the more kinetically favorable 5-*exo* cyclization, albeit in slightly diminished yield.

Table 5-4. Alkene oxyacylation scope[a]

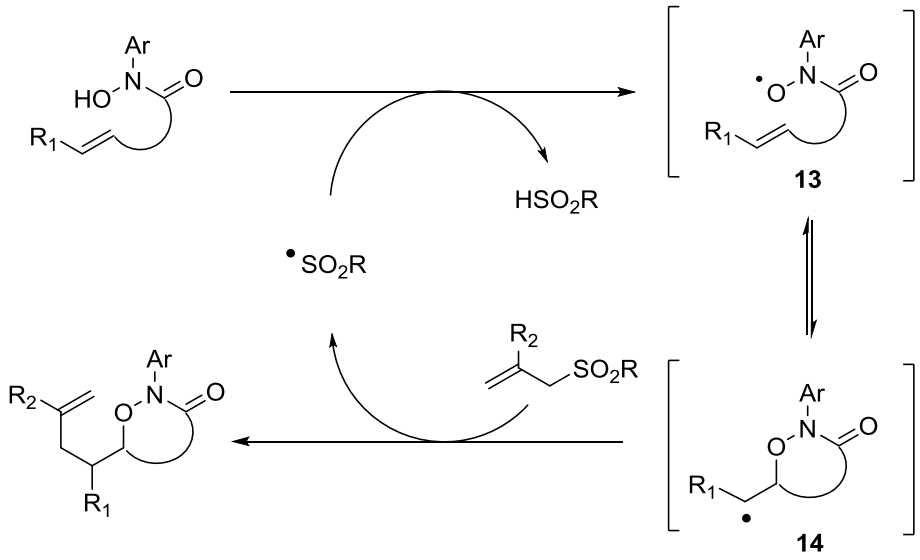
Entry	Substrate	Product	yield%[a]
1	 **1**		**19** 71%
2	 **5**		**20** 55% (60:40 d.r.)
3	 **11**		**21** 35%

[a] Yield over two steps: i) 5 equiv sulfonyl oxime ether, 0.5M in DMSO at 85°C ii) 4 equiv CSA in THF and 37% aq formaldehyde

5.3.4 Proposed Mechanism

We envision that the oxyallylation processes occurs via a similar mechanism to our previously developed dioxygenation and oxyamination reactions (**Figure 5-7**).[8] Following the formation of the amidoxyl radical **14**, a reversible cyclization step provides carbon-centered radical **15**. This intermediate then reacts with the allyl sulfone to form a new C-C bond and generate a sulfonyl radical. This furnishes the desired product and a species then can facilitate H-atom abstraction from the starting material to reinitiate the chain process

Figure 5-7. Proposed oxyallylation mechanism



5.4 Summary

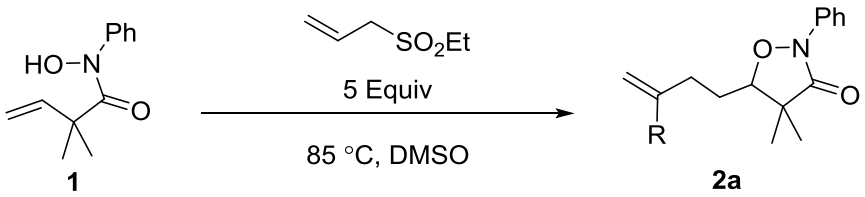
In conclusion, we have developed a radical-mediated approach to carbooxygenation encompassing a number of valuable difunctionalizations of alkenes. The transformations described include alkene oxyallylation, oxycyanation, and oxyacylation using unsaturated hydroxamic acids. These represent rare examples of direct alkene carbooxygenation reactions, and deliver highly functionalized, synthetically versatile small molecules from readily accessible compounds. In the course of these studies, we have also discovered the utility of hydrogen-bond donors in facilitating reactions of hydroxamic acids. These studies further increase the capabilities of hydroxamic acids in facilitating unique, radical-mediated alkene difunctionalizations.

5.5 Experimental Data

5.5.1 General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker model DRX 400, DRX 500, or a Bruker AVANCE III 600 CryoProbe (^{1}H NMR at 400, 500 or 600 MHz and ^{13}C NMR at 100, 126 or 151 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.28 ppm, C_6D_6 at 7.16 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, tdd = triplet of doublet of doublets, qd = quartet of doublets, m = multiplet, br. s. = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass Quattro II (triplequad) equipped with nanoelesctrospray ionization. Thin layer chromatography (TLC) was performed on SiliaPlate 250µm thick silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or ethanolic acidic *p*-anisaldehyde solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63 µm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, and dichloromethane were dried by passage through a column of neutral alumina under nitrogen prior to use. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

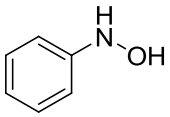
Table 5-5. Additive optimization for oxyallation of **1**



Entry	Additive	mol %	Time [h]	Yield [%]
1	$PhSO_2NH_2$	10	48	43
2	$PhSO_2NH_2$	20	40	52
3	$PhSO_2NH_2$	50	36	53
4	$PhSO_2NH_2$	100	36	52
5	$TolSO_2NHSO_2Tol$	50	40	32
6	trifluoro-methanesulfonic acid amide	50	10	18
7	1,4-benzoquinone	20	22	38
8	1,4-benzoquinone	50	20	44

All reactions were carried out according to oxyallylation general **Method A** outlined below.

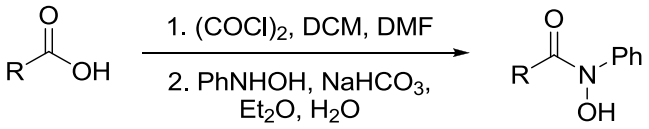
5.5.2 Compound Preparation



N-Phenylhydroxylamine was synthesized according to literature procedures.[13,14] Physical and spectral data were in accordance with literature data.[15]

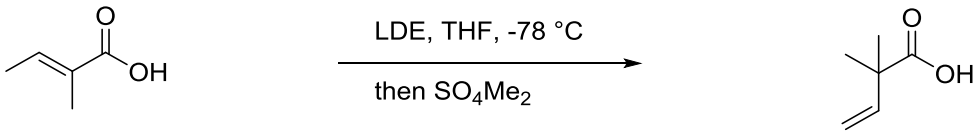
General Procedure for Preparation of *N*-Phenyl Hydroxamic Acids[3]

Note: All N-aryl hydroxamic acids should be purified promptly upon formation and stored neat at -40 ºC.



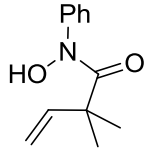
To a 0 ºC solution of carboxylic acid (1 mmol) in DCM (1.4 mL) and DMF (10 drops) was added oxalyl chloride (2 mmol) dropwise under an argon atmosphere. The solution was stirred at 0 ºC for 15 min. then warmed to room temperature for 40 min. The resultant yellow solution was evaporated almost to dryness under reduced pressure before sodium bicarbonate (2 mmol) was added and redissolved in H_2O/Et_2O (1 mL/2 mL). The solution was then again cooled to 0 ºC and phenylhydroxylamine (1 mmol) was added and the reaction was stirred at 0 ºC until phenylhydroxylamine has been consumed as visualized by TLC. The layers were separated, the aqueous layer was acidified with 1 M $NaHSO_4$ and extracted with Et_2O (x 3). The combined organic layers were then washed with brine, dried ($MgSO_4$), and concentrated to give an oil that was purified by flash chromatography to yield the corresponding *N*-phenyl hydroxamic acid.

Synthesis of 1



The corresponding carboxylic acid of **1** was synthesized via an alkylation of tiglic acid with dimethylsulfate as previously described.[2]

The procedure is as follows: Under a gentle stream of Ar, Hexanes was removed from a commercially available solution of n-BuLi (88.0 mL of a 1.52M solution, 133 mmol). The nearly dry reagent was cooled to -78 ºC, and taken up in THF (40 mL). Diethylamine (13.2 mL, 128 mmol, 2.1 equiv) was added to the cold solution and the resultant mixture was warmed to 0 ºC and stirred 15 min. The reaction mixture was cooled again to -78 ºC, tiglic acid (6.00 g, 59.9 mmol, 1.0 equiv) was added as a solution in THF (65 mL) before warming to 0 ºC and stirring for 30 min. The reaction mixture was cooled again to -78 ºC and a solution of dimethylsulfate (5.67 mL, 59.9 mmol, 1.0 equiv) in THF (125 mL) was added. The reaction mixture was allowed to come to rt, stirred 1 h and then quenched by slow addition of water. The reaction mixture was extracted with EtOAc (3 x), the combined organic layers discarded; the aqueous layer was acidified using conc. HCl until cloudiness persisted, extracted with EtOAc (4 x), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude acid product was purified via vacuum distillation to afford 2,2-dimethylbut-3-enoic acid (5.64 g, 82%) as a pale yellow liquid.



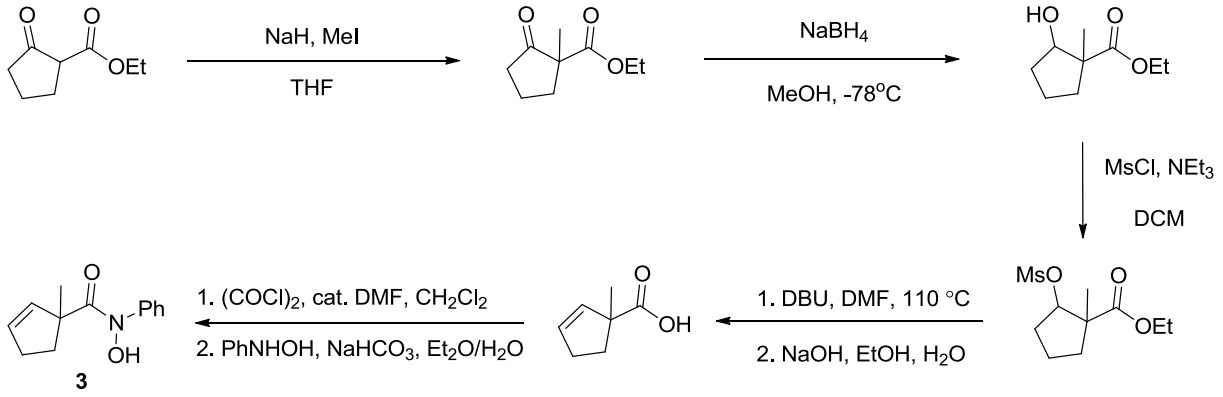
1

1 was synthesized via the general method in 58% yield (840.0 mg) as a pale yellow solid.

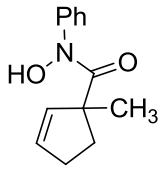
Analytical data for **1**: **^{1}H NMR** (500 MHz, CHLOROFORM-*d*) δ ppm 8.14 (br. s., 1 H) 7.47 (m, 2 H) 7.40 (m, 2 H) 7.34 (m, 1 H) 5.95 (m, 1 H) 4.97 (m, 2 H) 1.35 (s, 6 H) ppm; **^{13}C NMR** (126 MHz, METHYLENE CHLORIDE-d_2) 174.3, 143.2, 141.1, 128.6 (2 C), 127.3, 124.8, 112.3 (2 C), 45.2, 25.4 (2 C); **IR** (thin film, cm^{-1}) 3216, 2978, 2931, 1945, 1622, 1592, 1495, 1384, 1355, 1235,

1184, 1084, 1068, 913, 759, 701; **HRMS** (ESI) Calcd. for $[C_{12}H_{15}NO_2+Na]^+$ = 228.10, Found = 228.10. (For NMR spectra see ref. 2)

Synthesis of 3, and general route to 5 and 7



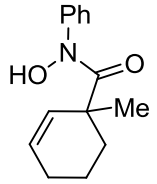
The corresponding carboxylic acid of **3** was synthesized according the procedure developed by S. Pichlmair *et. al.*[16] outlined above. Procedure for the saponification of ethyl 1-methylcyclopent-2-enecarboxylate follows: The crude ester (1.16 g, 7.52 mmol) was heated to reflux in a solution of EtOH (8 mL) and NaOH (400 mg, 10 mmol) for 2 h. The reaction mixture was diluted with Et_2O and acidified with 1N HCl. The aqueous layer was extracted with Et_2O (4 x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give crude acid product that was purified via flash chromatography (20% EtOAc/Hexanes) to give 1-methylcyclopent-2-enecarboxylic acid (619 mg, 4.91 mmol, 65%) as a pale liquid. Physical and spectral data were in accordance with literature data.[17]



3

3 was synthesized via the general procedure in 75% yield (641.0 mg) as pale yellow solid.

Analytical data for **3**: **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 8.53 (br. s., 1 H) 7.41 (m, 5 H) 5.56 (m, 1 H) 5.50 (m, 1 H) 2.39 (m, 1 H) 2.29 (m, 2 H) 1.70 (ddd, *J*=12.63, 7.58, 4.89 Hz, 1 H) 1.30 (s, 3 H) ppm; **^{13}C NMR** (126 MHz, METHYLENE CHLORIDE-d_2) 175.5, 141.1, 135.6 (2 C) 130.3, 128.6 (2 C), 127.3, 124.8, 56.2, 35.7, 31.3, 24.5; **IR** (thin film, cm^{-1}) 3200, 2930, 2850, 1622, 1592, 1494, 1454, 1381, 1065, 921, 758, 694; **LRMS** (ESI) Calcd. for $[C_{13}H_{15}NO_2+Na]^+$ = 240.10, Found = 240.10. (For NMR spectra see ref. 2)



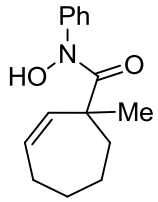
5

The corresponding carboxylic acid of **5** was synthesized via the same route as 1-methylcyclopent-2-enecarboxylic acid (see above), beginning with the cyclohexane analog. **5** was synthesized via the general procedure in 80% yield (790.0 mg) as an off-white solid.

Analytical data for **5**: **^{1}H NMR** (CHLOROFORM-*d*, 500MHz): d = 8.74 (br. s, 1 H), 7.32 - 7.45 (m, 5 H), 5.44 (m, 1 H), 5.10 - 5.39 (m, 1 H), 2.26 - 2.37 (m, 1 H), 1.80 - 1.97 (m, 2 H), 1.56 - 1.68 (m, 2 H), 1.38 (ddd, *J*=12.8, 8.4, 4.2 Hz, 1 H), 1.29 (s, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 126 MHz) 174.0, 140.2, 130.9, 128.8, 128.6, 127.4, 127.2, 43.4, 33.9, 26.4, 24.5, 19.5 ; **IR** (thin

film, cm^{-1}) 3205, 3036, 2933, 2871, 2834, 1615, 1591, 1491, 1452, 1355, 1306, 1066, 758, 695; **LRMS** (ESI) Calcd. for $[C_{14}H_{17}NO_2+Na]^+$ = 254.12, Found = 254.14.

Hydroxamic acid **15** was prepared via the same route as **5,** but alkylation was carried out using allyl bromide.



7

The corresponding carboxylic acid of **7** was synthesized via the same route as 1-methylcyclopent-2-enecarboxylic acid (see above), beginning with the cycloheptane analog.

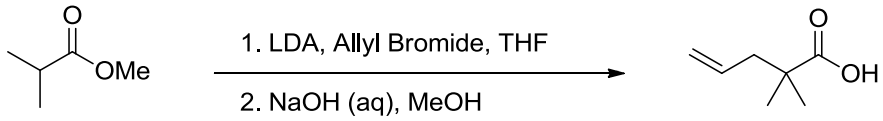
Spectral data for 1-methylcyclohept-2-enecarboxylic acid : **^{1}H NMR** (CHLOROFORM-*d*, 400MHz): δ = 10.94 - 12.90 (m, 1 H), 5.84 (dt, *J*=11.7, 6.0 Hz, 1 H), 5.61 (dd, *J*=11.7, 0.6 Hz, 1 H), 2.14 - 2.21 (m, 2 H), 2.02 - 2.11 (m, 1 H), 1.77 - 1.84 (m, 2 H), 1.50 - 1.75 (m, 3 H), 1.38 (s, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 101MHz): δ = 183.8, 134.4, 132.3, 48.4, 37.0, 28.1, 27.4, 27.1, 25.8 ppm.

7 was synthesized via the general procedure in 61% yield (544.0 mg) as an off-white solid.

Analytical data for **7**: **^{1}H NMR** (CHLOROFORM-*d*, 400MHz): δ = 7.30 - 7.60 (m, 5 H), 5.45 (br. s., 1 H), 4.91 - 5.28 (m, 1 H), 2.27 (ddd, *J*=13.5, 5.7, 3.6 Hz, 1 H), 1.72 - 2.09 (m, 4 H), 1.43 - 1.65 (m, 3 H), 1.32 - 1.39 (m, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 126 MHz) 174.4, 171.7, 171.2, 170.7, 140.6, 136.5, 136.0, 131.0, 128.7, 127.9, 126.0, 125.0, 124.7, 117.1, 117.0, 116.8, 87.5, 85.5, 85.4, 84.0, 51.0, 49.0, 48.3, 47.7, 38.3, 37.4, 34.8, 31.9, 30.7, 29.5, 28.3, 27.2, 26.5, 26.3, 23.8, 23.7 ppm (*Note*: Due to the high reactivity of this hydroxamic acid, it was only able to be

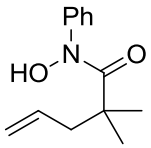
isolated in 90% purity; therefore oxyallylation reactions were performed immediately following isolation); **IR** (thin film, cm^{-1}) 3237, 3019, 2927, 2860, 1698, 1668, 1623, 1593, 1495, 1453, 1373, 1352, 757, 690; **LRMS** (ESI) Calcd. for $[C_{15}H_{19}NO_2+Na]^+$ = 268.13, Found = 268.15.

Synthesis of 9



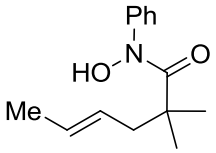
The corresponding carboxylic acid of **9** was synthesized according the procedure developed by Trost *et. al* [18] followed by base hydrolysis of the alkylated ester.

The procedure is as follows: A 2.5M solution of n-BuLi in Hexanes (12.9 mL, 32.3 mmol, 1.1 equiv) was added to a -78 ºC solution of diisopropylamine (4.6 mL, 32.3 mmol, 1.1 equiv) in THF (155 mL). The resultant solution was warmed to 0 ºC for 15 min, then cooled to -78 ºC and methyl isobutyrate (3.4 mL, 29.4 mmol, 1.0 equiv) added dropwise and stirred cold 1 h. Allyl bromide (2.5 mL, 29.4 mmol, 1.0 equiv) was added to the -78 ºC reaction mixture, stirred cold for 30 min and then allowed to slowly warm to rt overnight. The reaction mixture was then diluted with Et_2O, washed with 1M $NaHSO_4$ (3 x), brine, dried ($MgSO_4$) and concentrated *in vacuo* to provide methyl 2,2-dimethylpent-4-enoate (1.17 g, 30 % yield) as a yellow liquid. The crude ester (1.17 g, 8.23 mmol) was heated to reflux in a solution of MeOH (33 mL), water (8 mL) and NaOH (1.65 g, 41.1 mmol, 5.0 equiv) for 2 h. The reaction mixture was diluted with Et_2O and acidified with 1N HCl. The aqueous layer was extracted with Et_2O (4 x) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to give crude acid product (879.0 mg, 83%) that was used without further purification.



9

9 was synthesized via the general procedure in 79% yield (809.0 mg) as an orange oil that crystallizes upon scratching. Analytical data for **9**: **^{1}H NMR** (500 MHz, CHLOROFORM-*d*) δ = 8.85 (br. s., 1 H) 7.44 (m, 5 H) 5.79 (m, 1 H) 5.09 (m, 2 H) 2.32 (d, *J*=7.33 Hz, 2 H) 1.10 (s, 6 H) ppm; **^{13}C NMR** (126 MHz, CHLOROFORM-*d*) 173.9, 140.1, 134.3, 129.4, 129.2 (2 C), 128.2, 118.1 (2 C), 45.5, 42.4, 26.3 (2 C); **IR** (thin film, cm^{-1}) 3194, 2976, 1614, 1591, 1496, 1391, 1361, 1271, 1067, 997, 916, 761, 690; **LRMS** (ESI) Calcd. for $[C_{13}H_{17}NO_2+Na]^+$ = 242.12, Found = 242.12. (For NMR spectra see ref. 2)



11

The corresponding carboxylic acid of **11** was synthesized via an alkylation of methyl isobutyrate with crotyl bromide followed by base hydrolysis using literature procedures as with **9** (see above for general alkylation and hydrolysis procedures).

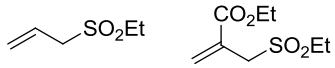
11 was synthesized via the general procedure in 78% yield (1.02 g) as an orange oil that crystallizes upon scratching.

Analytical data for **11**: **^{1}H NMR** (CHLOROFORM-*d*, 500MHz): δ = 8.68 - 9.08 (m, 1 H), 7.31 - 7.43 (m, 5 H), 5.43 - 5.63 (m, 1 H), 5.32 - 5.42 (m, 1 H), 2.21 - 2.35 (m, 2 H), 1.54 - 1.70 (m, 3 H), 1.04 - 1.15 (m, 6 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 126 MHz) 174.7, 140.6, 128.8,

128.4, 126.9, 126.7, 126.6, 125.8, 43.7, 42.9, 42.8, 37.5, 25.9, 25.8, 18.0, 13.0; **IR** (thin film, cm^{-1}) 3189, 2969, 2930, 1613, 1591, 1494, 1390, 1360, 1067, 968, 760, 701; **LRMS** (ESI) Calcd. for $[C_{14}H_{19}NO_2+Na]^+$ = 256.13, Found = 256.15.

5.5.3 General Oxyallylation Conditions

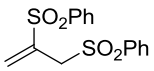
Method A (Sulfones i and ii)



i **ii**

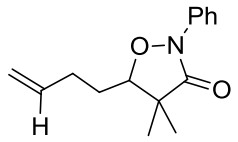
A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv) and sulfone **i** or **ii** (5.0 equiv) and benzene sulfonamide (0.5 equiv). The vial was then brought into a dry glovebox and the mixture was dissolved in de-gassed DMSO to make a 0.45M solution. The vial was fitted with a PTFE-lined screw cap, taken out of the glovebox, and allowed to stir at 85˚C. Upon disappearance of the hydroxamic acid substrate (24-50 h), as indicated by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), and extracted with CH_2Cl_2 (3 x 3mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.

Method B (Sulfone iii)



iii

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv) and sulfone **iii** (5.0 equiv) and benzene sulfonamide (0.5 equiv). The vial was then brought into a dry glovebox and the mixture was dissolved in de-gassed DMSO to make a 0.45M solution. The vial was fitted with a PTFE-lined screw cap, taken out of the glovebox, and allowed to stir at 85˚C. Upon disappearance of the hydroxamic acid substrate (24-50 h), as indicated by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), and extracted with CH_2Cl_2 (3 x 3mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting crude mixture was dissolved in EtOH (1-2 mL) and cooled to 0˚C to induce precipitation of unreacted sulfone. The sulfone was then filtered off, and the filtrate was concentrated under reduced pressure. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.

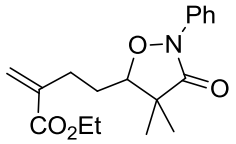


2a

2a was prepared via **Method A** using **1** (20.1 mg, 0.098 mmol), sulfone **i** (65.8 mg, 0.490 mmol), benzene sulfonamide (7.75 mg, 0.049 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **2a** (12.7 mg, 0.052 mmol, 53% yield) as a clear oil.

Analytical data for **2a**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.75 (d, *J* = 8.5 Hz, 2 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 5.90 (tdd, *J* = 6.7, 10.3, 17.0 Hz, 1 H), 5.19 - 5.04 (m, 2 H), 4.23 (dd, *J* = 3.3, 9.8 Hz, 1 H), 2.48 - 2.35 (m, 1 H), 2.28 (qd, *J* = 7.2, 14.5 Hz, 1 H), 1.96 - 1.82 (m, 1 H), 1.77 - 1.64 (m, 1 H), 1.29 (s, 3 H), 1.21 (s, 3 H) ppm; **^{13}C NMR**

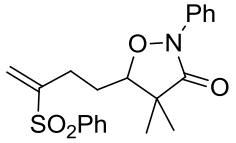
(CHLOROFORM-*d*, 100 MHz) 172.1, 137.2, 128.7, 124.4, 116.3, 115.8, 86.9, 46.2, 29.9, 27.1, 21.3, 17.7 ppm; **IR** (thin film, cm^{-1}) 3076, 2972, 1704, 1641, 1595, 1496, 1389, 1306, 1180, 914, 752; **LRMS** (ESI) Calcd. for $[C_{15}H_{19}NO_2+H]^+$ = 246.14, Found = 246.13.



2b

2b was prepared via **Method A** using **1** (20.3 mg, 0.098 mmol), sulfone **ii** (98.1 mg, 0.490 mmol), benzene sulfonamide (7.8 mg, 0.049 mmol) in DMSO (200 μL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **2b** (17.3 mg, 0.054 mmol, 56% yield) as a clear oil.

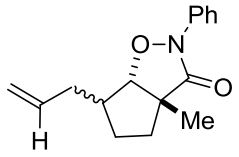
Analytical data for **2b**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.74 (d, *J* = 8.5 Hz, 2 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 7.16 (t, *J* = 1.0 Hz, 1 H), 6.27 (s, 1 H), 5.68 (s, 1 H), 4.30 - 4.19 (m, 3 H), 2.73 - 2.61 (m, 1 H), 2.53 (ddd, *J* = 6.5, 8.7, 14.7 Hz, 1 H), 2.01 - 1.79 (m, 2 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.29 (s, 3 H), 1.21 (s, 3 H); **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 171.9, 166.8, 136.9, 139.6, 137.2, 128.7, 125.7, 124.4, 116.3, 87.0, 60.8, 46.2, 28.6 , 26.8, 21.3, 17.7, 14.2 ppm; **IR** (thin film, cm^{-1}) 2972, 2932, 1710, 1631, 1594, 1495, 1388, 1362, 1306, 1177, 1025, 753, 690; **LRMS** (ESI) Calcd. for $[C_{18}H_{23}NO_4+H]^+$ = 318.16, Found = 318.23.



2c

2c was prepared via the **Method B** method on a 100mg scale using **1** (100.5 mg, 0.49 mmol), sulfone **iii** (560.1.6 mg, 1.70 mmol, 3.5 equiv), benzene sulfonamide (38.75 mg, 0.245 mmol) in DMSO (1.2 mL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 52 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **2c** (168.7 mg, 0.441 mmol, 90% yield) as a grey white residue.

Analytical data for **2c**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.93 (d, *J* = 7.3 Hz, 2 H), 7.66 (d, *J* = 8.8 Hz, 3 H), 7.57 (t, *J* = 1.0 Hz, 2 H), 7.38 (t, *J* = 7.8 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 6.47 (s, 1 H), 5.86 (s, 1 H), 4.11 (dd, *J* = 3.0, 10.0 Hz, 1 H), 2.70 - 2.58 (m, 1 H), 2.47 (td, *J* = 8.2, 16.0 Hz, 1 H), 1.96 - 1.76 (m, 3 H), 1.22 (s, 3 H), 1.13 (s, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 171.6, 149.4, 138.6, 137.0, 133.8, 129.4, 128.8, 128.3, 124.6, 124.5, 116.3, 86.2, 46.1, 26.4, 26.2, 21.3, 17.6 ppm; **IR** (thin film, cm^{-1}) 2973, 2252, 2090, 1643, 1494, 1364, 1305, 1137, 1081, 909 ; **LRMS** (ESI) Calcd. for $[C_{21}H_{23}NO_4S+H]^+$ = 386.13, Found = 386.21.

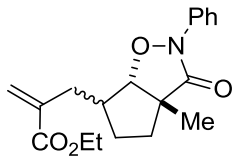


4a

4a was prepared via **Method A** using **3** (20.0 mg, 0.092 mmol), sulfone **i** (65.1 mg, 0.460 mmol), benzene sulfonamide (7.6 mg, 0.046 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 48 h. The crude reaction mixture was worked up and purified by flash chromatography (15% EtOAc/hexanes) to afford **4a** (7.8 mg, 0.052 mmol, 30% yield) as a clear oil.

Analytical data for **4a**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.42 - 7.36 (m, *J* = 7.5, 8.8 Hz, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 5.91 - 5.79 (m, 1 H), 5.16 - 5.08 (m, 2 H), 4.39 (d, *J* = 3.0 Hz, 1 H), 2.45 - 2.36 (m, 1 H), 2.36 - 2.21 (m, 2 H), 2.21 - 2.11 (m, 1 H), 2.01 (qd, *J* = 7.6, 13.1 Hz, 1 H), 1.79 (td, *J* = 7.7, 13.4 Hz, 1 H), 1.64 - 1.52 (m, 2 H), 1.48 (s, 2 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100MHz): 171.1, 137.1, 136.0, 128.7, 124.6, 116.7, 93.3, 55.0, 45.8, 36.6, 35.9, 29.6, 21.7 ppm; **IR** (thin film, cm^{-1}) 3073, 2961, 2931, 2871, 1697, 1594, 1495, 1458, 1376, 1307, 994, 915, 753, 690 ; **LRMS** (ESI) Calcd. for $[C_{16}H_{19}NO_2+H]^+$ = 258.14, Found = 258.12.

See attached 2D spectra for stereochemical assignment.



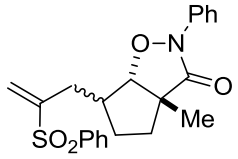
4b

4b was prepared via **Method A** using **3** (20.0 mg, 0.092 mmol), sulfone **ii** (94.8 mg, 0.460 mmol), benzene sulfonamide (7.6 mg, 0.046 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 48 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **4b** (16.6 mg, 0.050 mmol, 55% yield) as a clear yellow oil.

Analytical data for **4b**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.74 (d, *J* = 7.8 Hz, 2 H), 7.38 (t, *J* = 1.0 Hz, 2 H), 7.15 (t, *J* = 1.0 Hz, 1 H), 6.30 (s, 0 H), 5.65 (s, 1 H), 4.38 (d, *J* = 3.3 Hz, 1 H), 4.28 - 4.17 (m, 2 H), 2.60 - 2.47 (m, 2 H), 2.47 - 2.37 (m, 1 H), 2.32 (td, *J* = 7.0, 13.7 Hz, 1 H), 2.06 - 1.92 (m, 1 H), 1.81 (td, *J* = 7.4, 13.6 Hz, 1 H), 1.56 (td, *J* = 6.7, 13.4 Hz, 1 H), 1.49 (s,

3 H), 1.32 (t, *J* = 7.2 Hz, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 171.0, 166.9, 138.8, 137.0, 128.7, 126.3, 124.6, 116.7, 93.3, 60.9, 54.8, 45.3, 35.6, 34.6, 29.6, 21.9, 14.2 ppm; **IR** (thin film, cm^{-1}) 2961, 2872, 1710, 1630, 1594, 1494, 1459, 1375, 1306, 1189, 1155, 1024, 952, 734, 690; **LRMS** (ESI) Calcd. for $[C_{16}H_{23}NO_4+H]^+$ = 330.16, Found = 330.32.

Stereochemical assignment based on analogy to **4a**.



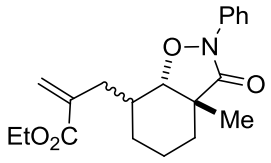
4c

4c was prepared via **Method B** using **3** (20.1 mg, 0.092 mmol), sulfone **iii** (148.1 mg, 0.460 mmol, 5 equiv), benzene sulfonamide (7.2 mg, 0.046 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 48 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **4c** as a mixture with some residual sulfone. The yield was determined by NMR using 2,4,6 trimethoxybenzene as an internal standard.

Analytical data **4c**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.91 (d, *J* = 8.3 Hz, 2 H), 7.70 (d, *J* = 7.8 Hz, 2 H), 7.65 (d, *J* = 7.5 Hz, 1 H), 7.59 - 7.52 (m, 4 H), 7.40 (t, *J* = 8.0 Hz, 2 H), 7.18 (t, *J* = 1.0 Hz, 1 H), 6.52 (s, 1 H), 5.89 (s, 1 H), 4.22 (d, *J* = 2.8 Hz, 1 H), 2.56 - 2.40 (m, 2 H), 2.39 - 2.20 (m, 2 H), 2.04 - 1.90 (m, *J* = 7.5, 13.3 Hz, 1 H), 1.68 (td, *J* = 7.5, 13.6 Hz, 1 H), 1.50 - 1.39 (m, 2 H), 1.37 (s, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100MHz): 170.5, 148.6, 138.8, 136.9, 133.8, 129.4, 128.8, 128.3, 124.8, 124.6, 116.7, 92.9, 54.9, 44.3, 52.5, 31.9, 29.7, 21.6 ppm;

IR (thin film, cm^{-1}) 3065, 2927, 2251, 1694, 1593, 1494, 1449, 1379, 1305, 1139, 1081, 912, 750, 690; **LRMS** (ESI) Calcd. for $[C_{22}H_{23}NO_4S+H]^+$ = 398.13, Found = 398.20

Stereochemical assignment based on analogy to **4a**.



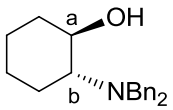
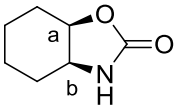
6b

6b was prepared via **Method A** using **5** (20.3 mg, 0.086 mmol), sulfone **ii** (88.6 mg, 0.430 mmol), benzene sulfonamide (6.5 mg, 0.043 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **6b** (20.9 mg, 0.059 mmol, 69% yield) as a clear oil. **6b** was isolated as a 58:42 mixture of inseparable diastereomers.

Analytical data for **6b**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.74 (t, *J* = 7.7 Hz, 2 H), 7.39 (dt, *J* = 4.8, 8.0 Hz, 2 H), 7.15 (dt, *J* = 4.4, 7.3 Hz, 1 H), 6.28 (dd, *J* = 1.4, 12.9 Hz, 1 H), 5.77 - 5.49 (m, 1 H), 4.25 (q, *J* = 7.0 Hz, 1 H), 4.18 - 3.95 (dd, *cis J*=2.8, *trans J*=8.4 Hz, 1 H), 4.15-4.01 (m, 1H), 2.80 - 2.44 (m, 2 H), 2.42 - 2.22 (m, 1 H), 2.05 - 1.83 (m, 1 H), 1.76 (dd, *J* = 3.4, 9.7 Hz, 1 H), 1.70 - 1.57 (m, 3 H), 1.40 - 1.30 (m, 4 H), 1.26 (s, 2 H), 1.19 (t, *J* = 7.0 Hz, 2 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100MHz): 172.6, 170.5, 167.0, 166.9, 138.8, 137.7, 137.6, 137.5, 128.8, 128.7, 127.4, 126.7, 124.3, 116.3, 116.2, 88.7, 84.5, 60.8, 60.7, 47.6, 45.6, 37.7, 37.0, 34.9, 34.3, 31.4, 29.9, 29.7, 28.2, 26.8, 23.7, 21.8, 20.8, 16.7, 14.2, 14.1 ppm; **IR** (thin film, cm^{-1}) 2934, 2863, 1710, 1629, 1594, 1495, 1457, 1363, 1303, 1213, 1159, 1024, 967, 753, 690; **LRMS** (ESI) Calcd. for $[C_{20}H_{25}NO_4+H]^+$ = 343.18, Found = 343.20.

Based on the coupling constants reported for *trans* and *cis* aminoalcohols of cyclohexanes as well as with analogous compounds previously reported by our group,[19] the diastereomer exhibiting the greater coupling constant suggests a *trans* relationship for substituted 6-membered rings.

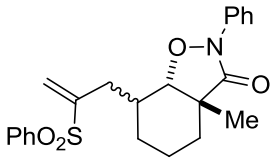
Table 5-6. Literature examples of *J* values for *trans* vs. *cis* O- and N-functionality on cyclohexanes

	 *trans* 2-(dibenzylamino)cyclohexanol	 *cis* hexahydrobenzo[*d*]oxazol-2(*3H*)-one
H_a	3.52 ppm, 1H (dt, *J* = 3.7, 9.3 Hz)	4.6 ppm, 1H (dt, *J* = 6 Hz)
H_b	2.36 ppm, 1H (dt, *J* = 3.0, 10.1 Hz)	3.70 ppm, 1H (q, *J* = 6 Hz)

The reported values of H_a and H_b for *trans*-2-(dibenzylamino)cyclohexanol[20] show that a large coupling constant (~10 Hz) suggests a *trans* substitution pattern.

Conversely, *cis*-hexahydrobenzo[*d*]oxazol-2(*3H*)-one[21] demonstrates that a smaller coupling constant (~6 Hz or fewer) would be evidence of a *cis* substitution pattern.

6b shows a doublet of doublets at 4.18 - 3.95 ppm with coupling constants of *J*=2.8 and *J*=8.4 Hz. Based on the evidence above, the isomer with the smaller coupling constant (2.8 Hz) suggests a *cis* configuration, while the isomer with the larger coupling constant (8.4 Hz) is suggestive of the *trans* diastereomer.

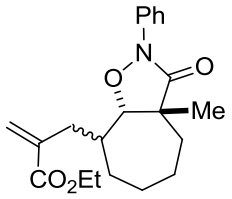


6c

6c was prepared via **Method B** using **5** (20.0 mg, 0.086 mmol), sulfone **iii** (96.9 mg, 0.300 mmol, 3.5 equiv), benzene sulfonamide (6.8 mg, 0.043 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **6c** (29.7 mg, 0.072 mmol, 84% yield) as a grey white residue. **6c** was isolated as a 52:48 mixture of inseparable diastereomers.

Analytical data for **6c**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.96 - 7.90 (m, 1 H), 7.77 - 7.54 (m, 5 H), 7.48 - 7.32 (m, 3 H), 7.23 - 7.09 (m, 1 H), 6.53 - 6.44 (m, 1 H), 5.96 - 5.69 (m, 1 H), 4.09 - 3.77 (dd, 1H, *cis J*=2.8, *trans J*=8.4), 2.93 - 2.31 (m, 2 H), 2.29 - 1.90 (m, 1 H), 1.77 - 1.46 (m, 4 H), 1.44 - 1.20 (m, 4 H), 1.18 (s, 2 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz at 320 K): 172.3, 170.0, 147.7, 147.3, 138.9, 138.7, 137.5, 137.3, 133.8, 133.6, 129.4, 129.2, 128.9, 128.8, 128.3, 128.2, 128.1, 126.8, 126.7, 126.0, 125.9, 124.6, 124.5, 116.2, 116.1, 88.5, 88.4, 83.7, 83.6, 47.6, 45.4, 36.7, 34.4, 33.7, 32.9, 31.2, 29.7, 27.0, 26.8, 23.8, 23.7, 21.6, 20.6, 16.6, 16.5 ppm; **IR** (thin film, cm^{-1}) 3064, 2935, 2862, 1703, 1594, 1496, 1458, 1447, 1381, 1363, 1304, 1142, 1081, 968, 914, 750, 689; **LRMS** (ESI) Calcd. for $[C_{23}H_{25}NO_4S+H]^+$ = 412.15, Found = 412.24.

Stereochemistry was assigned by analogy to **6b**.

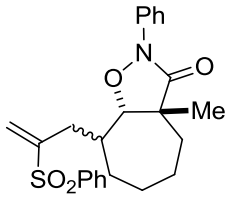


8b

8b was prepared via **Method A** using **7** (21.6 mg, 0.088 mmol), sulfone **ii** (90.6 mg, 0.440 mmol), benzene sulfonamide (6.9 mg, 0.044 mmol) in DMSO (200 μL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **8b** (20.8 mg, 0.055 mmol, 63% yield) as a clear oil. **8b** was isolated as a 69:31 mixture of inseparable diastereomers.

Analytical data for **8b**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.85 - 7.70 (m, 2 H), 7.45 - 7.34 (m, 2 H), 7.21 - 7.11 (m, 1 H), 6.29 (s, 1 H), 5.68 - 5.56 (m, 1 H), 4.27 - 4.16 (m, 2 H), 4.39 and 4.09-4.07 (s, indicates *cis* and d, *J*=8.4 Hz indicates *trans*, 1 H), 2.91 - 2.46 (m, 2 H), 2.36 - 2.04 (m, 2 H), 2.03 - 1.51 (m, 5 H), 1.50 - 1.20 (m, 10 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100MHz): 171.6, 166.9, 138.8, 138.7, 136.9, 128.7, 128.6, 127.2, 126.6, 124.6, 124.4, 116, 7, 116.4, 91.3, 88.9, 91.3, 88.9, 60.8, 60.7, 50.6, 50.3, 40.1, 39.0, 37.6, 37.1, 36.9, 31.7, 30.1, 29.5, 28.4, 28.2, 24.6, 24.1, 23.3, 22.8, 14.2, 14.1 ppm; **IR** (thin film, cm^{-1}) 2927, 2857, 1710, 1594, 1495, 1367, 1304, 1187, 1157, 1025, 952, 753, 690; **LRMS** (ESI) Calcd. for $[C_{21}H_{27}NO_4+H]^+$ = 358.19, Found = 358.25.

Based on the previously demonstrated preference of cyclic hydroxamic acids to form the *trans* diastereomer,[7] a *trans* assignment was made by analogy as the major product of **8b**.

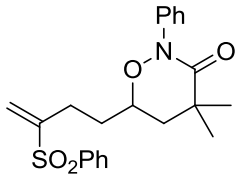


8c

8c was prepared via **Method B** using (20.2 mg, 0.081 mmol), sulfone **iii** (91.9 mg, 0.290 mmol, 3.5 equiv), benzene sulfonamide (6.4 mg, 0.041 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **8c** (29.7 mg, 0.069 mmol, 86% yield) as a grey white residue. **8c** was isolated as a 72:28 mixture of inseparable diasteremoers.

Analytical data for **8c**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.96 - 7.33 (m, 9 H), 7.23 - 7.13 (m, 1 H), 6.55 - 6.45 (m, 1 H), 5.87 - 5.74 (m, 1 H), 4.21 and 3.90-3.78 (s, and d, *J*=8.8 Hz, 1 H), 2.86 - 2.42 (m, 2 H), 2.19 - 2.02 (m, 2 H), 1.88 - 1.55 (m, 4 H), 1.54 - 1.43 (m, 1 H), 1.42 - 1.26 (m, 2 H), 1.23 (s, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 171.2, 148.7, 138.8, 136.8, 133.8133.5, 129.4, 129.2, 128.8, 128.7, 128.3, 126.1, 124.7, 126.6, 115.7, 116.4, 91.1, 88.1, 50.5, 50.2, 38.6, 37.4, 36.8, 36.4, 34.2, 31.6, 29.7, 29.0, 28.2, 28.0, 24.7, 24.0, 23.4, 23.5 ppm; **IR** (thin film, cm^{-1}) 3065, 2929, 2857, 2251, 1696, 1593, 1494, 1449, 1385, 1306, 1145, 1081, 957, 913, 749, 690 ; **LRMS** (ESI) Calcd. for $[C_{24}H_{27}NO_4S+H]^+$ = 426.14, Found = 426.22.

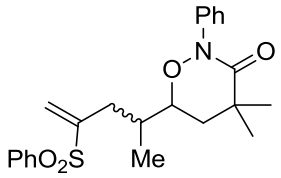
Stereochemistry was assigned by analogy to **8b**.



10

10 was prepared via **Method B** using **9** (20.3 mg, 0.091 mmol), sulfone **iii** (296.1 mg, 0.910 mmol, 10 equiv), benzene sulfonamide (6.8 mg, 0.046 mmol) in DMSO (200 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 52 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **10** as a mixture with some residual sulfone. The yield (37%) was determined by NMR using 2,4,6 trimethoxybenzene as an internal standard.

Analytical data for **10**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.89 (d, *J* = 8.0 Hz, 1 H), 7.71 - 7.63 (m, 1 H), 7.62 - 7.52 (m, 4 H), 7.35 (t, *J* = 8.0 Hz, 2 H), 7.22 - 7.12 (m, 1 H), 6.38 (s, 1 H), 5.71 (s, 1 H), 4.28 - 4.16 (m, 1 H), 2.58 - 2.33 (m, 2 H), 2.04 (dd, *J* = 7.3, 13.6 Hz, 1 H), 1.99 - 1.80 (m, 2 H), 1.76 (dd, *J* = 8.5, 13.8 Hz, 1 H), 1.40 (s, 3 H), 1.35 (s, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100MHz): 174.7, 149.6, 139.6, 138.7, 133.7, 129.3, 128.6, 128.3, 125.1, 124.1, 119.6, 79.1, 42.7, 39.1, 33.3, 27.2, 26.1, 25.9 ppm; **IR** (thin film, cm^{-1}) 3065, 2967, 2930, 2870, 1677, 1593, 1490, 1448, 1390, 1354, 1305, 1144, 1081, 954, 913, 750, 690, 573; **LRMS** (ESI) Calcd. for $[C_{22}H_{25}NO_4S+H]^+$ = 400.15, Found = 400.19



12

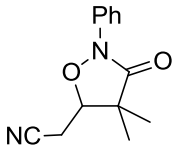
12 was prepared via **Method B** using **11** (20.5 mg, 0.085 mmol), sulfone **iii** (276.1 mg, 0.850 mmol, 10 equiv), benzene sulfonamide (6.8 mg, 0.043 mmol) in DMSO (200 μL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 52 h. The crude reaction mixture was worked up and purified by flash chromatography (20% EtOAc/hexanes) to afford **12** as a mixture with some residual sulfone. The yield (41%) was determined by NMR using 2,4,6 trimethoxybenzene as an internal standard.

Analytical data for **12**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.88 (t, *J* = 7.7 Hz, 2 H), 7.64 (t, *J* = 7.3 Hz, 2 H), 7.59 - 7.51 (m, 3 H), 7.41 - 7.30 (m, 2 H), 7.21 - 7.12 (m, 1 H), 6.44 (d, *J* = 18.1 Hz, 1 H), 5.72 (d, *J* = 10.8 Hz, 1 H), 4.11 - 3.89 (m, 1 H), 2.81 - 2.44 (m, 1 H), 2.38 - 2.01 (m, 3 H), 2.00 - 1.85 (m, 2 H), 1.41 (s, 4 H), 1.34 (s, 3 H), 1.02 - 0.89 (m, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100MHz): δ = 174.6, 174.5, 148.4, 148.2, 139.5, 139.4, 138.7, 133.7, 133.6, 129.7, 129.6, 129.3, 129.2, 128.8, 128.6, 128.4, 128.3, 127.9, 125.8, 125.3, 125.1, 119.6, 83.9, 82.9, 40.6, 40.6, 40.3, 39.0, 38.9, 35.8, 35.44, 33.6, 33.1, 27.8, 27.7, 26.2, 26.1, 14.5, 14.0 ppm; **IR** (thin film, cm^{-1}) 3065, 2971, 2932, 1676, 1593, 1490, 1449, 1390, 1354, 1304, 1142, 1081, 961, 912, 751, 690, 571; **LRMS** (ESI) Calcd. for $[C_{23}H_{27}NO_4S+H]^+$ = 414.17, Found = 414.24.

5.5.4 General Oxycyanation Conditions

A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv) and *p*-toluenesulfonyl cyanide (TsCN, 3.0 equiv) and dissolved in specified nitrile solvent to make a 0.5M solution. While not necessary for reactivity, the addition of specified radical initiators in some reactions resulted in improved product yields and reaction times, and is indicated below when used. The vial was fitted with a PTFE-lined screw cap and argon was bubbled through the solution for 5-8 min. The reaction was allowed to stir under 1 atm argon at

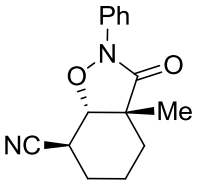
the specified temperature. Upon disappearance of the hydroxamic acid substrate, as indicated by TLC analysis, the solvent was removed under reduced pressure. The resulting cyclic hydroxamate was purified by flash chromatography using the specified solvent system.



13

13 was prepared using **1** (20.0 mg, 0.0974 mmol), TsCN (53.0 mg, 0.292 mmol), DLP (10 mol %, 3.9 mg, 0.0097 mmol) in EtCN (210 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 21 h. The solvent was removed from the crude reaction mixture under reduced pressure and the crude material was purified by flash chromatography (33% EtOAc/hexanes) to afford **13** (13.7 mg, 0.0595 mmol, 61 % yield) as a clear, colorless oil.

Analytical data for **13**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.76 - 7.68 (m, 2 H), 7.47 - 7.35 (m, 2 H), 7.24 - 7.15 (m, 1 H), 4.56 (dd, *J* = 5.8, 7.8 Hz, 1 H), 2.87 (dd, *J* = 8.0, 17.1 Hz, 1 H), 2.75 (dd, *J* = 5.8, 16.8 Hz, 1 H), 1.45 - 1.40 (m, 3 H), 1.29 (s, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 169.92, 136.56, 128.92, 125.19, 116.58, 115.47, 82.15, 46.35, 21.98, 17.77, 17.51 ppm; **IR** (thin film, cm^{-1}) 3068, 2974, 2932, 2254, 1708, 1594, 1494, 1392, 1361, 1308, 1180, 1149, 1083, 1051, 910, 754, 690; **LRMS** (ESI) Calcd. for $[C_{13}H_{14}N_2O_2+H]^+$ = 231.11, Found = 230.97.

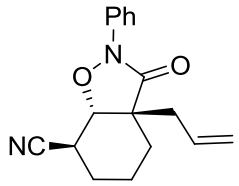


14

14 was prepared using **5** (100.0 mg, 0.433 mmol), TsCN (235.1 mg, 0.259 mmol, 3.0 equiv.) in MeCN (930 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 40 h with the addition of two portions of DLP (17.1mg, 0.043 mmol). The solvent was removed from the crude reaction mixture under reduced pressure and the crude material was purified by flash chromatography (20% EtOAc/hexanes) to afford **14** as a 60:40 mixture of diastereomers (less polar isomer 30.9 mg, and more polar isomer 25.5 mg, 0.220 mmol total, 51% yield) as a colorless oil.

Analytical data for **14 major** *:* **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.76 - 7.68 (m, 2 H), 7.45 - 7.37 (m, 2 H), 7.24 - 7.16 (m, 1 H), 4.48 (d, *J* = 7.8 Hz, indicates *trans*, 1 H), 2.91 (ddd, *J* = 4.1, 7.7, 10.5 Hz, 1 H), 2.26 - 2.17 (m, 1 H), 2.16 - 2.06 (m, 1 H), 1.83 - 1.64 (m, 2 H), 1.55 - 1.37 (m, 2 H), 1.46 (s, 3 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 169.13, 136.99, 128.96, 125.15, 119.83, 116.47, 83.36, 46.93, 30.16, 30.01, 26.18, 22.26, 20.51 ppm; **IR** (thin film, cm^{-1}) 3067, 2935, 2869, 2246, 1833, 1710, 1594, 1494, 1455, 1363, 1306, 1180, 1142, 1014, 973, 912, 754, 688; **LRMS** (ESI) Calcd. for $[C_{15}H_{16}N_2O_2+H]^+$ = 257.13, Found = 257.12.

Analytical data for **14 minor***:* **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.81 - 7.74 (m, 2 H), 7.47 - 7.37 (m, 2 H), 7.24 - 7.15 (m, 1 H), 4.44 (d, *J* = 3.3 Hz, indicates *cis*, 1 H), 2.98 (ddd, *J* = 3.3, 5.0, 12.3 Hz, 1 H), 2.12 - 1.95 (m, 2 H), 1.91 - 1.81 (m, 1 H), 1.81 - 1.68 (m, 2 H), 1.50 - 1.37 (m, 1 H), 1.36 - 1.30 (m, 3 H)) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 170.42, 136.86, 128.87, 125.03, 118.32, 116.53, 80.51, 44.99, 28.88, 28.17, 24.64, 19.63, 16.96 ppm; **IR** (thin film, cm^{-1}) 2928, 2867, 2246, 1707, 1593, 1495, 1458, 1364, 1305, 1154, 980, 903, 754, 691; **LRMS** (ESI) Calcd. for $[C_{15}H_{16}N_2O_2]^+$ = 257.13, Found = 257.12.



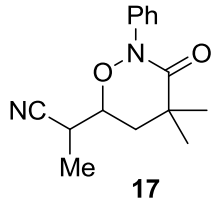
16

16 was prepared using **15** (60.0 mg, 0.233 mmol), TsCN (126.8 mg, 0.699 mmol), DLP (10 mol %, 9.4 mg, 0.023 mmol) in EtCN (500 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 36 h. The solvent was removed from the crude reaction mixture under reduced pressure and the crude material was purified by flash chromatography (gradient of 15-20-25% EtOAc/hexanes) to afford **16** as a 68:32 mixture of diastereomers (less polar isomer 23.2 mg, 0.0822 mmol, and more polar isomer 10.8 mg, 0.0383, total 52% yield) as a colorless oil.

Analytical data for **16 major**: **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.77 - 7.70 (m, 2 H), 7.46 - 7.39 (m, 2 H), 7.25 - 7.17 (m, 1 H), 5.92 - 5.77 (m, 1 H), 5.30 - 5.21 (m, 2 H), 4.62 (d, *J* = 8.3 Hz, indicates *cis*, 1 H), 2.88 (ddd, *J* = 4.3, 8.2, 11.4 Hz, 1 H), 2.56 - 2.51 (m, 2 H), 2.24 - 2.16 (m, 1 H), 2.15 - 2.07 (m, 1 H), 1.85 - 1.74 (m, 1 H), 1.68 - 1.50 (m, 3 H), 1.45 - 1.30 (m, 1 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 167.89, 136.85, 131.37, 128.95, 125.21, 120.71, 119.99, 116.52, 80.93, 50.53, 39.54, 30.42, 27.84, 26.22, 20.67 ppm; **IR** (thin film, cm^{-1}) 3076, 2927, 2865, 2246, 1703, 1593, 1494, 1455, 1368, 1307, 1206, 1142, 1082, 987, 919, 754, 689; **LRMS** (ESI) Calcd. for $[C_{17}H_{18}N_2O_2+H]^+$ = 283.15, Found = 283.15.

Analytical data for **16 minor***:* **^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.81 - 7.72 (m, 2 H), 7.42 (t, *J* = 8.0 Hz, 2 H), 7.25 - 7.16 (m, 1 H), 5.95 - 5.79 (m, 1 H), 5.28 - 5.15 (m, 2 H), 4.63 (d, *J* = 3.3 Hz, indicates *cis*, 1 H), 2.94 (ddd, *J* = 3.3, 5.3, 11.8 Hz, 1 H), 2.64 (dd, *J* = 6.1, 14.2 Hz, 1 H), 2.39 (dd, *J* = 8.7, 14.4 Hz, 1 H), 2.11 - 1.96 (m, 2 H), 1.90 - 1.71 (m, 3 H), 1.59 (s, 3 H), 1.56 - 1.45 (m, 1 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 100 MHz) 169.09, 136.69, 132.19, 128.83,

125.07, 119.84, 118.38, 116.57, 77.43, 48.09, 36.03, 28.31, 27.95, 24.13, 19.57 ppm; **IR** (thin film, cm^{-1}) 3075, 2925, 2857, 2247, 1832, 1705, 1594, 1494, 1456, 1365, 1305, 1177, 1143, 988, 914, 754, 690; **LRMS** (ESI) Calcd. for $[C_{17}H_{18}N_2O_2+H]^+$ = 283.15, Found = 283.15.



17

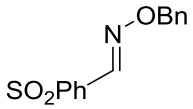
17 was prepared using **11** (25.0 mg, 0.107 mmol), TsCN (58.3 mg, 0.321 mmol), (*t*BuON)$_2$ (1.9 mg, 0.011 mmol, 10 mol % x3) in EtCN (250 µL). The reaction was completed, as indicated by TLC, after heating at 60 ºC for 28 h. The solvent was removed from the crude reaction mixture under reduced pressure and the crude material was purified by flash chromatography (20% EtOAc/hexanes) to afford **17** (less polar isomer 6.6 mg, 0.0255 mmol and more polar isomer 8.4 mg, 0.0325 mmol, 54% combined yield) as clear, colorless oils.

Analytical data for **17 TS: ^{1}H NMR** (600MHz, CHLOROFORM-d) δ = 7.61 (d, *J* = 8.7 Hz, 2 H), 7.40 (t, *J* = 7.7 Hz, 2 H), 7.26 - 7.17 (m, 1 H), 4.36 (q, *J* = 7.9 Hz, 1 H), 3.04 (quin, *J* = 7.1 Hz, 1 H), 2.28 (dd, *J* = 7.3, 13.7 Hz, 1 H), 2.11 (dd, *J* = 8.7, 13.9 Hz, 1 H), 1.48 (s, 3 H), 1.46 (d, *J* = 7.2 Hz, 3 H), 1.43 (s, 3 H); **^{13}C NMR** (CHLOROFORM-*d*, 151 MHz) 174.70, 139.07, 128.70, 125.66, 119.94, 119.47, 79.50, 40.02, 39.03, 30.58, 27.01, 25.33, 14.66 ppm; **IR** (thin film, cm^{-1}) 3064, 2926, 2244, 1679, 1594, 1491, 1391, 1355, 1300, 1177, 1059, 965, 755, 692; **LRMS** (ESI) Calcd. for $[C_{15}H_{18}N_2O_2+H]^+$ = 259.14, Found = 259.12.

Analytical data for **17 LS: ^{1}H NMR** (400MHz, CHLOROFORM-d) δ = 7.73 (d, *J* = 8.7 Hz, 2 H), 7.44 - 7.38 (m, 2 H), 7.23 - 7.17 (m, 1 H), 4.38 - 4.33 (m, 1 H), 2.93 (quin, *J* = 7.1 Hz, 1 H), 2.16 (dd, *J* = 7.5, 13.9 Hz, 1 H), 2.01 (dd, *J* = 9.0, 13.9 Hz, 1 H), 1.49 (s, 3 H), 1.47 (d, *J* = 6.8 Hz, 3

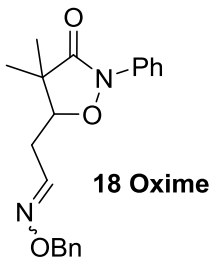
H), 1.42 (s, 3 H); **^{13}C NMR** (CHLOROFORM-*d*, 151 MHz) 174.33, 139.16, 128.73, 125.47, 119.50, 79.78, 40.56, 39.11, 30.63, 27.34, 25.54, 14.31 ppm; **IR** (thin film, cm^{-1}) 3064, 2926, 2244, 1679, 1594, 1491, 1391, 1355, 1300, 1177, 1059, 965, 755, 692; **LRMS** (ESI) Calcd. for $[C_{15}H_{18}N_2O_2+H]^+$ = 259.14, Found = 259.12.

5.5.4.1 General Oxyacylation Conditions



iv

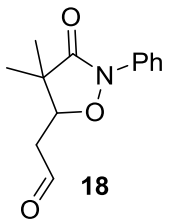
A new 1-dram vial containing a magnetic stir bar was charged with unsaturated hydroxamic acid (1.0 equiv), sulfone **iv** (5.0 equiv) and benzene sulfonamide (0.5 equiv). The vial was then brought into a dry glovebox and the mixture was dissolved in de-gassed DMSO to make a 0.45M solution. The vial was fitted with a PTFE-lined screw cap, taken out of the glovebox, and allowed to stir at 85˚C. Upon disappearance of the hydroxamic acid substrate (24-50 h), as indicated by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (10 mL), and extracted with CH_2Cl_2 (3 x 3mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting crude mixture was dissolved in EtOH (1-2 mL) and cooled to 0˚C to induce precipitation of the unreacted sulfone which was removed by filtration. The filtrate was then concentrated under reduced pressure, dissolved in THF (1-3mL) and camphorsulfonic acid (4.0 equiv) and aqueous formaldehyde (37%, 10.0 equiv) were added. The reaction was stirred at room temperature, overnight. The mixture was then diluted with Et_2O (10 mL), washed with $NaHCO_3$ (5 mL), and extracted with Et_2O (2x10mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified using column chromatography in the specified solvent system



18 Oxime

18 Oxime was prepared according to the general procedure (but isolated prior to hydrolysis) on a 100mg scale using **1** (100.1 mg, 0.49 mmol), sulfone **iv** (673.5 mg, 2.45 mmol), benzene sulfonamide (50 mol %, 35.5 mg, 0.25 mmol) in DMSO (1.2 mL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 52 h. The crude material was purified by flash chromatography (16% hexanes/DCM) to afford **18 Oxime** as a 50:50 mixture of E/Z isomers (121.4 mg, 0.075 mmol, 72 % yield) as a clear, grey residue.

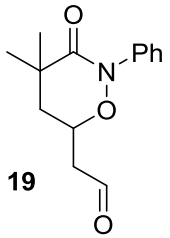
Analytical data for **18 Oxime**: ^{1}H NMR (600MHz, CHLOROFORM-d) δ = 7.76 - 7.66 (m, 2 H), 7.60 (dd, *J* = 5.3, 6.8 Hz, 0.5 H), 7.45 - 7.32 (m, 7 H), 7.20 - 7.12 (m, 2 H), 6.94 (t, *J* = 5.3 Hz, 0.5 H), 5.18 (s, 1H), 5.13 (2, 1 H), 4.43 (ddd, *J* = 4.6, 9.1, 11.6 Hz, 1 H), 2.88 - 2.73 (m, 1 H), 2.69 (ddd, *J* = 5.5, 9.3, 14.9 Hz, 0.5 H), 2.64 - 2.54 (m, 0.5 H), 1.29 (d, *J* = 11.4 Hz, 3 H), 1.22 (d, *J* = 3.7 Hz, 3 H); **^{13}C NMR** (CHLOROFORM-*d*, 150MHz): 171.3, 171.2, 146.3, 146.2, 137.5, 137.4, 136.9, 136.8, 128.8, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 124.7, 124.6, 116.4, 116.3, 84.9, 84.6, 76.2, 75.9, 46.3, 28.8, 25.2, 21.4, 21.3, 17.7, 17.6 ppm; **IR** (thin film, cm^{-1}) 3064, 3032, 2970, 2930, 2875, 1702, 1594, 1494, 1459, 1388, 1361, 1307, 1180, 1021, 902, 752, 659; **LRMS** (ESI) Calcd. for $[C_{20}H_{22}N_2O_3+H]^+$ = 339.16, Found = 339.07



18

18 was prepared from the hydrolysis of **18 Oxime** (36.0 mg, 0.106 mmol), using CSA (100.2 mg, 0.371 mmol), formaldehyde (0.75 mL, 37% aq, 1.06 mmol) in THF (1.1mL). The reaction was completed, as indicated by TLC, after stirring at rt overnight. The crude material was purified by flash chromatography (15% Et_2O/Pentanes) to afford **18** (23.1 mg, 0.098 mmol, 93 % yield, 71% over 2 steps) as a clear oil.

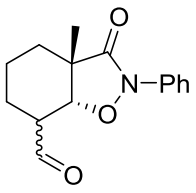
Analytical data for **18**: **^{1}H NMR** (600MHz, CHLOROFORM-d) δ = 9.93 (s, 1 H), 7.70 (d, *J* = 8.1 Hz, 2 H), 7.39 (t, *J* = 7.9 Hz, 2 H), 7.17 (t, *J* = 7.3 Hz, 1 H), 4.84 (dd, *J* = 3.9, 9.0 Hz, 1 H), 2.97 (ddd, *J* = 1.8, 9.2, 17.2 Hz, 1 H), 2.75 (ddd, *J* = 1.1, 3.7, 17.6 Hz, 1 H), 1.34 (s, 3 H), 1.22 (s, 3 H); **^{13}C NMR** (CHLOROFORM-*d*, 150MHz): 197.8, 179.9, 136.8, 128.8, 124.8, 116.4, 81.8, 46.0, 42.2, 21.3, 18.0ppm; **IR** (thin film, cm^{-1}) 2975, 2875, 2733, 1726, 1701, 1593, 1494, 1464, 1388, 1360, 1308, 1041, 918, 754; **LRMS** (ESI) Calcd. for $[C_{13}H_{15}NO_3+H+MeOH]^+$ = 266.13, Found = 266.04.



19

19 was prepared according to the general procedure using **9** (20.3. mg, 0.091 mmol), sulfone **iv** (246.2.4 mg, 0.912 mmol), benzene sulfonamide (50 mol %, 6.8 mg, 0.046 mmol) in DMSO (210 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 48 h. The reaction was worked up according to the general procedure and the crude product was subjected to the hydrolysis conditions: CSA (100.2 mg, 0.371 mmol), formaldehyde (0.75 mL, 37% aq, 1.06 mmol) in THF (1.2 mL µL). The reaction was completed, as indicated by TLC, after stirring at RT overnight. The crude material was purified by flash chromatography (15% Et_2O/Pentanes) to afford **19** (7.9 mg, 0.031 mmol, 34% over 2 steps) as a clear oil.

Analytical data for **19**: **^{1}H NMR** (600MHz, CHLOROFORM-d) δ = 9.85 (s, 1 H), 7.67 (d, *J* = 7.7 Hz, 2 H), 7.38 (t, *J* = 8.1 Hz, 2 H), 7.18 (t, *J* = 7.3 Hz, 1 H), 4.91 (dq, *J* = 5.1, 7.9 Hz, 1 H), 3.03 (ddd, *J* = 1.7, 8.1, 17.8 Hz, 1 H), 2.80 - 2.74 (m, 1 H), 2.25 (dd, *J* = 7.3, 13.9 Hz, 1 H), 1.87 (dd, *J* = 8.4, 13.9 Hz, 1 H), 1.45 (s, 3 H), 1.41 (s, 3 H); **^{13}C NMR** (CHLOROFORM-*d*, 150MHz): 200.7, 174.4, 139.2, 128.7, 125.5, 119.5, 115.9, 74.8, 41.4, 39.1, 26.8, 25.3, 23.2 ppm; **IR** (thin film, cm^{-1}) 2925, 2360, 1725, 1676, 1592, 1489, 1353, 1302, 1059, 754, 690; **LRMS** (ESI) Calcd. for $[C_{14}H_{17}NO_3 + H + MeOH]^+$ = 280.15, Found = 380.02.



20

20 was prepared according to the general procedure using **5** (31.2. mg, 0.134 mmol), sulfone **iv** (177.4 mg, 0.671 mmol), benzene sulfonamide (50 mol %, 10.3 mg, 0.067 mmol) in DMSO (210 µL). The reaction was completed, as indicated by TLC, after heating at 85 ºC for 36 h. The reaction was worked up according to the general procedure and the crude product was subjected to the hydrolysis conditions: CSA (100.2 mg, 0.371 mmol), formaldehyde (0.75 mL, 37% aq, 1.06 mmol) in THF (1.2mL). The reaction was completed, as indicated by TLC, after stirring at rt overnight. The crude material was purified by flash chromatography (15% Et_2O/Pentanes) to afford **20** as a 60:40 mixture of diastereomers (19.1 mg, 0.074 mmol, 54% over two steps) as a clear oil. The diastereomers were later separated by additional flash chromatography (7% Et_2O/Pentanes).

Analytical data for **20 Major**: **^{1}H NMR** (600MHz, CHLOROFORM-d) δ = 9.82 (s, 1 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 7.40 (t, *J* = 7.9 Hz, 2 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 4.70 (d, *J* = 6.6 Hz, 1 H; indicates *trans*), 2.77 - 2.71 (m, 1 H), 2.27 - 2.21 (m, 1 H), 2.10 - 2.04 (m, 1 H), 1.74 - 1.68 (m, 1 H), 1.47 - 1.38 (m, 6 H) ppm; **^{13}C NMR** (CHLOROFORM-*d*, 150 MHz): 200.7, 170.1, 137.3, 128.9, 124.8, 116.3, 81.5, 50.3, 46.9, 30.8, 22.9, 22.4, 20.9 ppm; **IR** (thin film, cm^{-1}) 2928, 2858, 1705, 1594, 1494, 1458, 1380, 1362, 1303, 975, 754; **LRMS** (ESI) Calcd. for $[C_{15}H_{17}NO_3$ +H +MeOH$]^+$ = 292.15, Found = 292.07.

Analytical data for **20 Minor**: **^{1}H NMR** (600MHz, CHLOROFORM-d) δ = 9.91 (s, 1 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 7.39 (t, *J* = 7.7 Hz, 2 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 4.75 (d, *J* = 2.9 Hz, 1 H indicates *cis*), 2.64 (td, *J* = 3.8, 12.7 Hz, 1 H), 2.03 - 1.97 (m, 1 H), 1.93 - 1.87 (m, 1 H), 1.81 (dq, *J* = 3.5, 13.1 Hz, 1 H), 1.76 - 1.72 (m, 2 H), 1.47 - 1.42 (m, 1 H), 1.35 (s, 3 H)ppm; **^{13}C NMR** (CHLOROFORM-*d*, 150 MHz): 200.6, 171.3, 137.1, 128.9, 128.8, 124.8, 116.4, 116.3, 81.6, 48.5,

45.4, 29.6, 20.4, 19.6, 16.6 ppm; **IR** (thin film, cm^{-1}) 3001, 2985, 1706, 1592, 1493, 1461, 1384, 1359, 1300, 975, 754; **LRMS** (ESI) Calcd. for $[C_{15}H_{17}NO_3 + H + MeOH]^+$ = 292.15, Found = 292.07.

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