1. C-C BOND FORMATION VIA SOFT ENOLIZATION AND UMPOLUNG-LIKE CHEMISTRY
2. ELECTROPHILIC FLUORINATION OF ORGANOZINC REAGENTS

by
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ABSTRACT

Synthetic methodology development towards convenient C-C bond and C-F bond formation is a desirable synthetic tool for industry and academia. Using commercially available substrates towards chemical transformations is often a strategy used to simplify the process of synthesizing compounds. This dissertation focuses on the synthetic methodology development of C-C and C-F bond formation for broad applicational utility.

This dissertation will discuss two synthetic strategies towards C-C bond formation, soft enolization and Umpolung-like chemistry. The direct synthesis of 1,3-diketones and β-keto thioesters in good yields and with wide substrate tolerance was possible using our soft enolization strategy using crude acyl chlorides. Another C-C bond strategy explored was an Umpolung-like approach towards α-functionalization of ketones.

Ketones are synthetically important functional group and have wide applicational uses within chemistry and biology. The α-functionalization of ketones and their derivatives via addition of their corresponding (aza) enolates to alkyl halides is a fundamental synthetic transformation but has been historically less explored despite its potential widespread utility. Our approach uses a novel β-silylated azoalkenes intermediate towards *anti*-diastereoselective α-alkylation of ketones.

In addition, we explored a streamlined approach towards monofluorohydrocarbon formation via electrophilic fluorination of organozinc compounds. We hope this will have wide applicational utility as C-F bonds are important within agrochemistry and pharmaceutical chemistry.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

.

LIST OF SCHEMES

LIST OF ABBREVIATIONS

1-D NOE	one-dimensional nuclear Overhauser effect spectroscopy
Ac	acetyl
DMF	dimethylformamide
THF	tetrahydrofuran
EDG	electron donating group
ESI	electron spray ionization
Et	ethyl
GC	gas chromatography
GC-MS	gas chromatography mas
HRMS	high resolution mass spectrometry
t-Bu	*tert*-butyl
Ph	phenyl
iPr	*iso*-propy
Me	methyl
L_n	ligands
ppm	parts per million
TMSCl	trimethylsilyl chloride
TBDMSCl	*tert*-butyldimethylsilyl chloride
LDA	lithium diethylamide
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
SET	single electron transfer
Equiv	equivalent

CHAPTER 1

CARBON-CARBON BOND FORMATION THROUGH SOFT ENOLIZATION AND UMPOLUNG-LIKE APPROACH

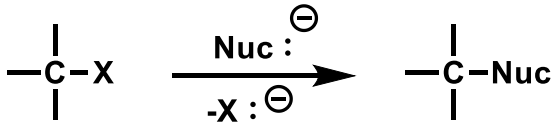
1.1 Introduction

Carbon-carbon bond formation is one of the most important synthetic transformations.[1] Disconnection strategies used by synthetic chemists to achieve the desired carbon-carbon bond formation can be broken down into many approaches[1-3] but the focus of this chapter will be on substitution and addition reactions.[4] Two types of carbon-carbon bond reactions will be discussed in detail. First, soft enolization will be reviewed for formation of 1,3-diketones and β-keto thioesters. Second, Umpolung-like approach towards diastereocontrolled α-alkylation of ketones will be discussed.[5]

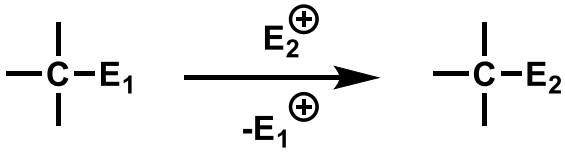
A substitution reaction towards carbon-carbon bond formation is defined as the displacement of one functional group or moiety with another functional group or moiety.[1,4] There are two main types of substitution reaction based on the type of 'attacking' or 'incoming' functional group: nucleophilic substitution and electrophilic substitution. [4] Nucleophilic aliphatic substitution occurs if 'attaching' molecule is a nucleophile, which is a species possessing valence electrons for new bond formation (Scheme 1.1). Electrophilic aliphatic substitution is somewhat analogous to nucleophilic substitution except both the leaving group and moiety displacing it are electron deficient Lewis acids (Scheme 1.2). Carbon-carbon bond formation is a driving force for both reactions as it is thermodynamically favorable with carbon-carbon bond strength being between 174 to 230 kcal/mol.[7] To date there are no examples of electrophilic aliphatic substitution affording 1,3-diketones and β-keto thioesters. Nucleophilic aliphatic substitution reactions however are widely used towards their preparation. The 1,3-dicarbonyl motifs is of interest as it is widely represented in natural products, pharmaceuticals, and other biologically relevant compounds in either their native or derivative form.[8] A common

synthetic method used to form carbon-carbon bonds is through conventional enolate chemistry, which is a subset of nucleophilic aliphatic substitution.[4]

Scheme 1.1 Nucleophilic Substitution



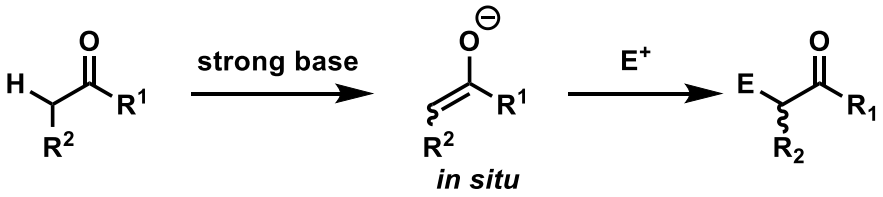
Scheme 1.2 Electrophilic Substitution



Conventional enolate chemistry or hard enolization is a synthetic method where a strong base ($pK_a > 30$) can irreversibly deprotonate the α-proton of a carbonyl moiety to create a nucleophile *in situ* (Scheme 1.3).[1] The *in situ* formed enolate can then react with an electrophile such as an alkyl halide or acyl chloride to form a new carbon-carbon bond. Hard enolization has been used to form a wide range of structural motifs but this chapter will focus on its use to form 1,3-dicarbonyl compounds. The Claisen condensation is a synthetic transformation of using ester as an enolate precursor to react with another ester to form a 1,3-dicarbonyl molecule. The reaction is catalyzed by an alkoxide base to form the desired enolate *in situ*.[9] Variations of the Claisen reaction include the use of different acylating agent such as acyl chlorides,[10,11] esters,[60] amides[64] and enolate precursors such as ketones,[13,61,62] esters,[14] and thioesters.[12,63] However, drawbacks to this approach include low yields of the desired 1,3-dicarbonyl product and/or limited substrate scope. One of the limitations of using the Claisen condensation approach is that a relatively low concentration of the desired enolate is formed as the alkoxide

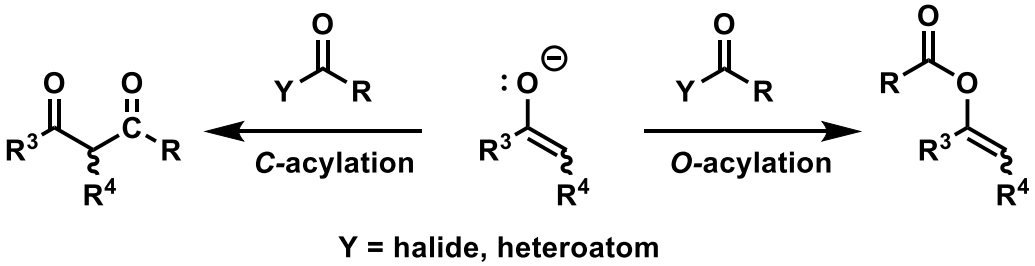
base is not sufficiently strong to irreversibly deprotonate the enolate precursor, in certain polar solvents. In organic solvent the α-proton pK_a of ketones is ~27, hence making an alkoxide base ineffective for irreversible deprotonation (pK_a ~30).[15,16] However, other arguments have been considered.[66]

Scheme 1.3 Hard Enolization



To overcome these limitations a strong base such as LDA[17] or KHMDS[18] can be used to irreversibly deprotonate the α-proton of the carbonyl compound under kinetic reaction conditions. While yields of the desired 1,3-dicarbonyl products are improved, there are still issues with deprotonation of acidic functionality elsewhere on the substrate. In addition, other competing reactions such as *O*-acylation and bis-acylation may interfere with the reaction. *O*-Acylation occurs via resonance structure where negative charge is placed on oxygen (Scheme 1.4).[19] In this case, the oxygen atom acts as the nucleophile instead of the α-carbon. Chemoselectivity can be established by *in situ* silylation of the enolate,[20] using a 'soft' acylating agent,[19,21] or using Lewis acids with preferential chelation to oxygen to mitigate *O*-acylation.[19] Hard enolization can also be labor intensive as it requires a step-wise approach at cold temperatures (-78 ^{o}C) to form the desired enolate. Furthermore, some substrates are base sensitive and may decompose under hard enolization conditions. To reduce these undesired outcomes, one can use soft enolization as an alternative method of generating enolates under mild reaction conditions.[22]

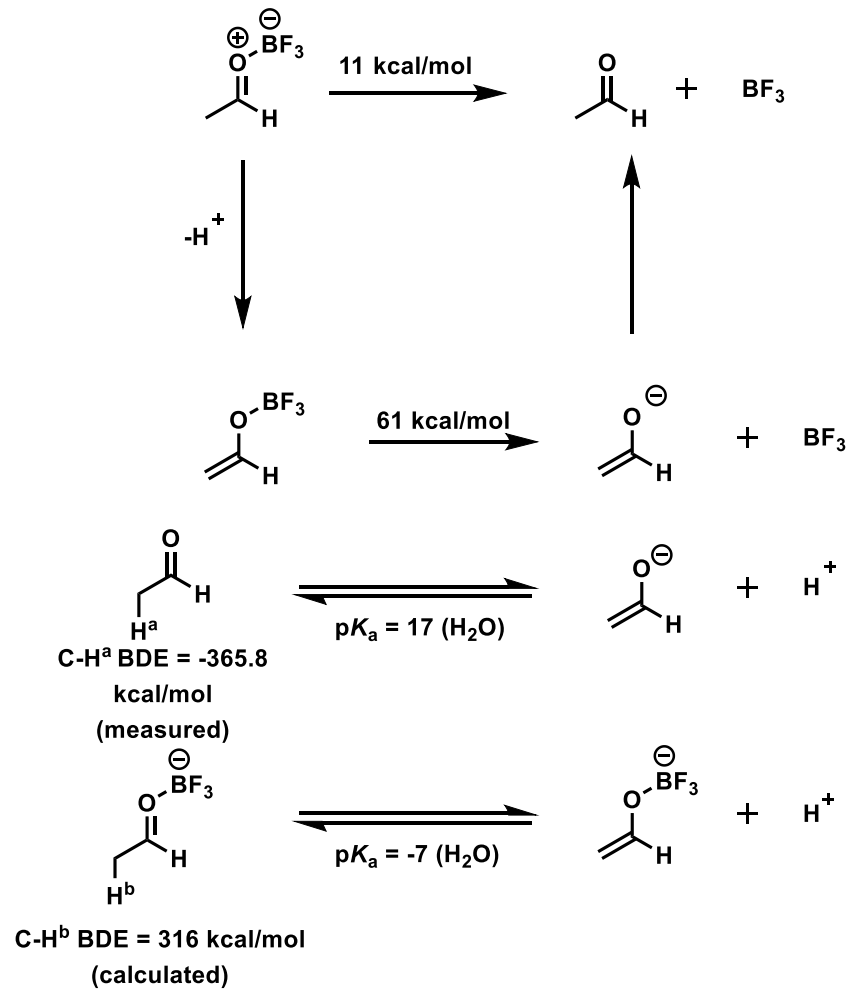
Scheme 1.4 *O*-Acylation vs *C*-Acylation



Soft enolization is a synthetic method where a weak base, typically a tertiary amine, is used in conjunction with a Lewis acid to form the enolate under thermodynamic reaction conditions.[1,22] Under soft enolization conditions the newly formed enolate is under equilibrium with the enolate precursor.[23] Due to the desired enolate being formed in the presence of its conjugate acid, it can develop into a convenient one pot methodology.[23] Many soft enolization reactions with varied temperatures, substrates, and Lewis acids have been performed in the last 50 years. Considerable research effort has been focused on the use of different Lewis acids including titanium,[24,65] boron,[25-27] magnesium,[28-30] and others.[31,32]

Ren and co-workers have shown that using BF_3 as a Lewis acid in conjunction with weak base Et_3N allows for deprotonation of the enolate precursor due to the pK_a of the α-proton being significantly reduced (Scheme 1.5).[33] They propose that the Lewis acid stabilizes the *in situ* formed enolate, making deprotonation by weak base more favorable and allowing formation of relatively higher concentration of the enolate. A favorable M-O (M= B, Ti, Sn, Mg) bond formation occurs thus stabilizing the enolate. Due to the interaction of the Lewis acid with the enolate, there is little to no *O*-acylation as the lone pair of the oxygen is blocked by the oxophilic Lewis acid.

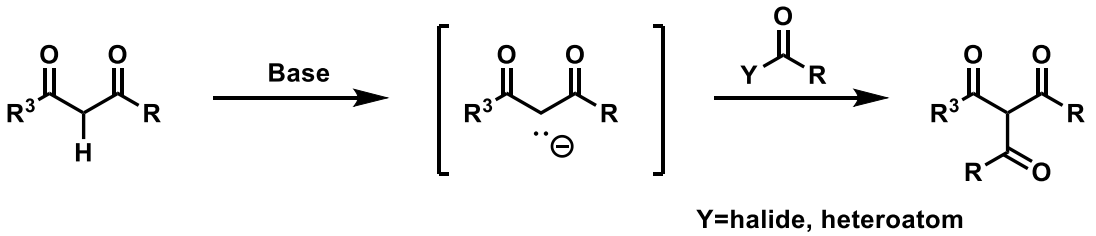
Scheme 1.5 Ren's Quantification of Acidity Enhancement by BF_3



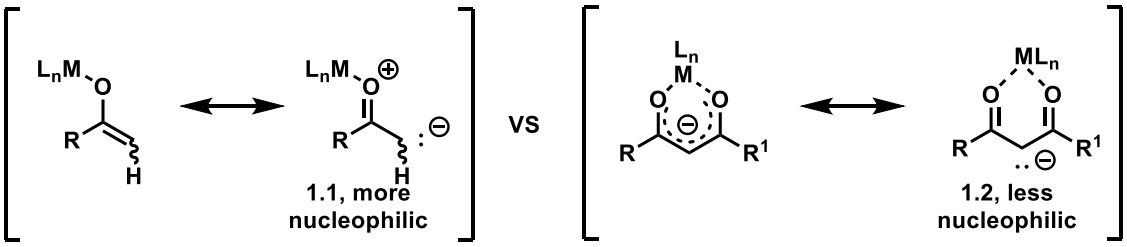
A drawback for such reaction design when forming 1,3-dicarbonyls is occurrence of bis-acylation. Under basic conditions, the α- proton of the 1,3-dicarbonyl product can be deprotonated by an additional base followed by reaction with an acylating agent (Scheme 1.6). This is possible as 1,3-dicarbonyls are substantially more acidic than simple monocarbonyl compounds. However, given the relatively weak nucleophilic nature of the dicarbonyl enolate, bis-acylation would not be expected to interfere. In the resonance form of the 1,3-dicarbonyl species structure, 1.2 (Scheme 1.7) is less Lewis basic than 1.1 as its lone pair is less available

due to being part of a more extended conjugate system. In addition, the intended ketone enolate will reform as it is under thermodynamic conditions (i.e. reversible deprotonation). Using soft enolization conditions allows for obtaining good yields of the desired products. Additionally, improved chemoselectivity may be observed as both *O*-acylation and bis-acylation are suppressed under these reaction conditions.

Scheme 1.6 General Scheme of Bis-Acylation



Scheme 1.7 Resonance Structures of Mono- vs Di-Carbonyl Species

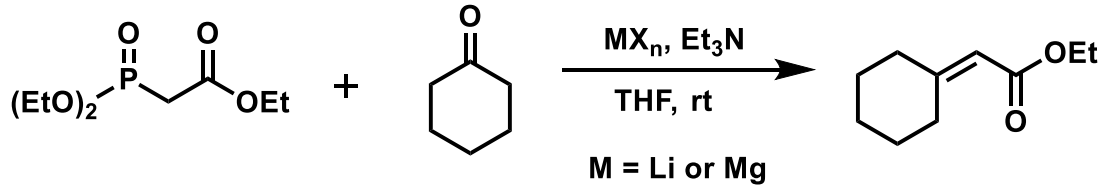


Among common Lewis acids, magnesium salts are of particular interest as they are easily accessible and cost effective to use.[23] Rathke's group has pioneered the use of magnesium in soft enolization to produce unsaturated esters and β-keto acids. They have developed a modified Horner-Wadsworth-Emmons reaction that couples cyclohexanone and phosphate ethyl ester to form α-β-unsaturated esters, using Et_3N and LiCl, LiBr, or $MgBr_2$ combination (Scheme 1.8).[28] They also showed that β-keto acids could be prepared using soft enolization conditions (Scheme 1.9).[34] Subsequently the Coltart group has reported the use of $MgBr_2$*OEt_2

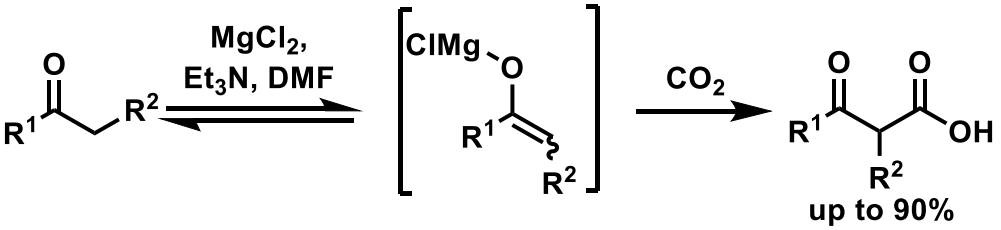
Lewis acid under soft enolization conditions towards β-keto thioester formation.[12,23] The same group has also prepared 1,3-diketones and other structural motifs by using similar conditions.[17,23,29,35-38]

The Coltart's group study on the reactivity pattern of various substrates as enolate precursors under soft enolization conditions showed that a balance needs to be achieved between Lewis basicity of the carbonyl moiety and the acidic nature of the α-proton to be deprotonated under soft conditions.[12] Thioesters are good enolate precursors under soft enolization conditions as the α-proton is sufficiently acidic to be deprotonated under these conditions. The reactivity trends of enolate formation under soft enolization using $MgBr_2*OEt_2$ was found to be as follows: aldehydes>thioesters > oxoesters>>amides> acyl chlorides. Amides and acyl chlorides are less prone to forming an enolate under soft enolization conditions. The acyl chloride is strongly acidic but weakly Lewis basic. Amides are strongly Lewis basic, however, their α-proton is weakly acidic. Oxoesters are more Lewis basic than thioesters; however, they are less acidic and thus are not susceptible to soft enolization by using $MgBr_2*OEt_2$ Lewis acid.

Scheme 1.8 Rathke's Modified Horner-Wadsworth Reaction

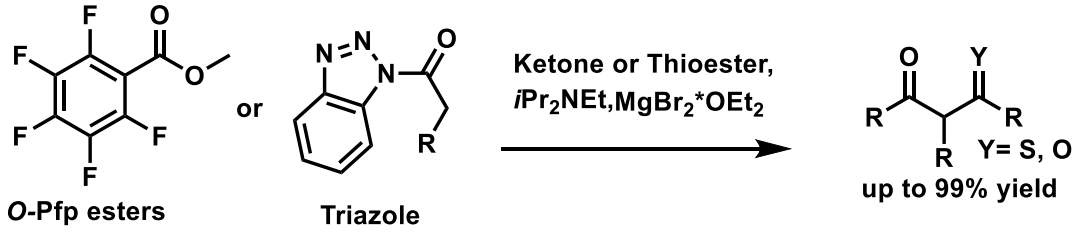


Scheme 1.9 Rathke's β-Keto Acid Formation



Many acylating agents can be used under soft enolization conditions. Coltart and co-workers found that *N*-acylbenzotriazoles and *O*-Pfp esters are good acylating agents (Scheme 1.10).[17] *N*-Acylpyrazoles and imidazole derivates can be effective acylating agents towards carbon-carbon bond formation as well.[39]

Scheme 1.10 Coltart's use of Different Acylating Agents



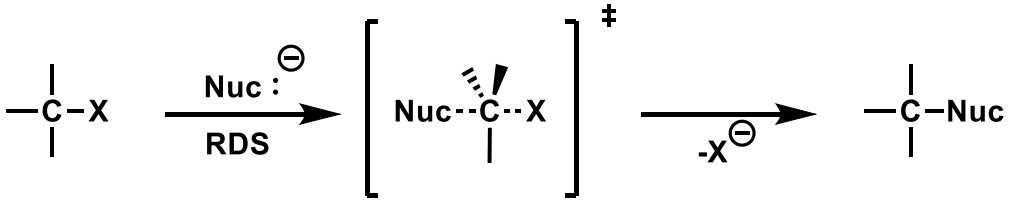
Reaction stereocontrol can be achieved under soft enolization.[18,40,41] The binding of the Lewis acid can enforce specific E or Z geometry of the enolate after α-deprotonation. Both enantiocontrolled or diastereocontrolled reactions have been developed for various structural motifs except for 1,3-diketone and β-keto thioester formation.

Nucleophilic aliphatic substitution proceeds via two possible mechanisms: S_N2 and S_N1. Bimolecular nucleophilic substitution (S_N2) is a reaction where both the concentration of the nucleophile and alkyl halide affects the rate of reaction.[1] In unimolecular nucleophilic substitution (S_N1) only the concentration of the electrophile dictates the rate of reaction. This is largely due to different mechanism of each process. The S_N2 reaction is a concerted reaction as shown in Scheme 1.11. Both the leaving group and substituent are bonding to the α-carbon in the transition state. Conversely in S_N1 the rate is controlled by the electrophile concentration as the rate determining step is loss of leaving group from the electrophile. Conventional enolate chemistry predominantly proceeds through an S_N2-like mechanism (Scheme 1.11). However, such transformations are intrinsically limited as tertiary, sp- and sp^2- hybridized alkyl halides

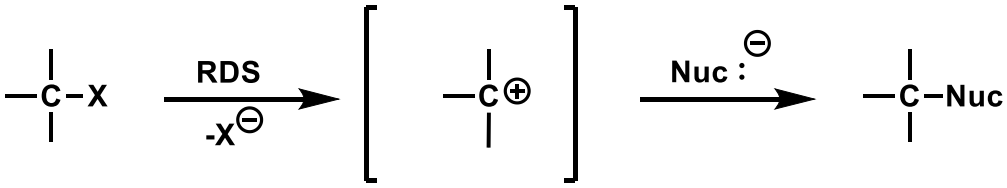
are unreactive under these reaction conditions. To circumvent the substrate scope limitation of such synthetic transformations researchers have developed new chemistry.

An addition reaction is defined as a reagent reacting to another substrate to form a new bond without a pre-existing atom leaving the molecule. The exact mechanisms of these reactions vary depending on the substrate but typically they can be classified as electrophilic or nucleophilic additions. An example of nucleophilic addition reaction is a substrate containing an alkene or alkyne attacked by a nucleophile forming a new bond without loss of a pre-existing atom.[4]

Scheme 1.11 General Scheme of S_N2 Reaction



Scheme 1.12 General Scheme of S_N1 Reaction

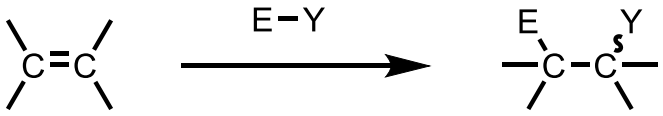


The difference between electrophilic and nucleophilic addition is mostly based on the electronic state of the reactant and reagent. In electrophilic addition to double and triple bonds the π bond is weak (~65 kcal /mol) and unless the double or triple bond is substituted with an electron withdrawing group, they are considered to be electron rich (Scheme 1.13).[4] Due to these features addition of an electrophilic reagent can occur readily. Nucleophilic addition varies in that an electron deficient carbon-carbon bond is susceptible to nucleophilic attack (Scheme 1.14). Examples of such reactions are activation of the alkene by complexed metal[42]

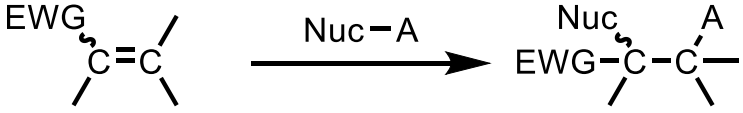
and Michael condensations.[43] Among the many addition strategies chemists have developed, the one of our interest is the Umpolung-like synthetic method towards carbon-carbon bond formation.

The term Umpolung is German for reversing polarity. It was originally coined by Seebach and further developed in a joint venture by Seebach and Corey.[44,45,48] The Umpolung approach can be developed to access different connectivity that is not available from classical enolate reactions. For example, 1,3- and 1,5-heteroatom skeletons can typically be prepared by employing established methods such as an aldol reaction, Claisen condensation, and others.[46] In contrast, 1,2-, 1,4-, and 1,6- heteroatom substitution patterns are difficult to achieve.[47] Before the development of the Umpolung approach chemists would simply use natural products (e.g. amino acids, oxalic acid, tartaric acid etc.) containing inaccessible substitution patterns as starting materials for synthesis.

Scheme 1.13 Electrophilic Addition



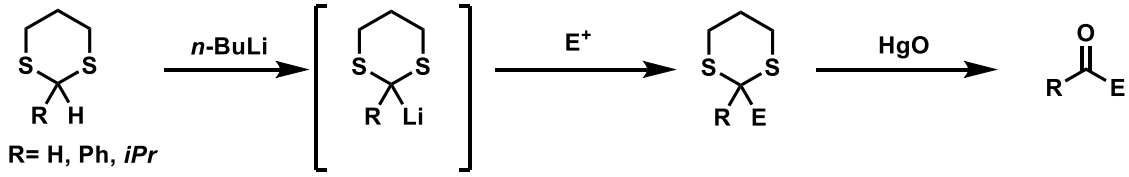
Scheme 1.14 Nucleophilic Addition



Seebach and Corey's first use of the Umpolung approach involved *in situ* lithiated dithiane as an acyl anion equivalent in reaction with alkyl halides followed by dithiane group removal to regenerate the carbonyl moiety (Scheme 1.15). The desired 1,2-carbon-carbon bond connection was then obtained.[48] Beyond the use of dithiane there have been a myriad of functional groups used as starting materials for Umpolung-type transformations. Azoalkenes or

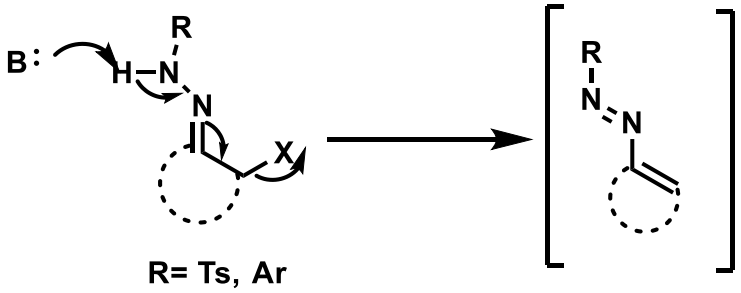
1,2-diaza-1,3-butadienes are viable starting materials for facile carbon-carbon bond formation using an Umpolung-like approach. Such substrates have gained popularity as their electrophilic α-carbon allows for different nucleophiles such as enolates and organometallic reagents to be used.[47] The advantage of using an Umpolung-like approach is that previously inaccessible starting materials such as 3° aliphatic halides, as well as sp- and sp^2- hybridized aliphatic halides can now be employed as the reaction is not limited by an S_N2 type mechanism.

Scheme 1.15 Corey-Seebach Umpolung Chemistry

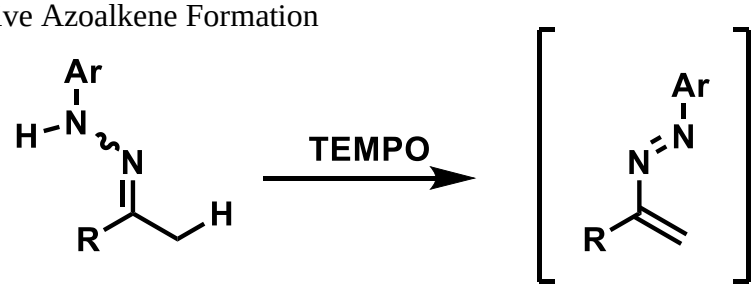


Various synthetic strategies have been used to form azoalkenes. α-Halo hydrazones can be employed under base catalysis to form the desired azoalkenes *in situ* (Scheme 1.16).[49] Another approach involves oxidation with TEMPO (Scheme 1.16) to make the *cis*-azoalkene isomer.[50] Lastly, ring opening of α-epoxides or α-aziridine hydrazones towards β-functionalized azoalkenes that can be isolated or used *in situ* is possible as well (Scheme 1.18).[51] Azoalkenes can participate in various transformations, including syntheses of heterocycles [47] or α-functionalization of ketones.[51,52]

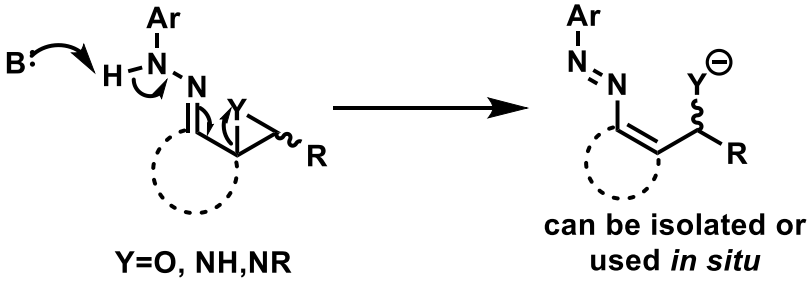
Scheme 1.16 Azoalkene formation with α-halo hydrazones



Scheme 1.17 Oxidative Azoalkene Formation

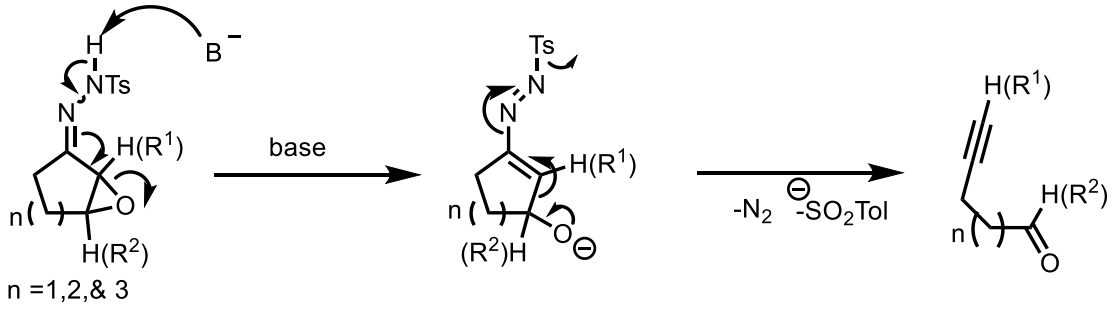


Scheme 1.18 Preparation of Azoalkenes via Ring Opening



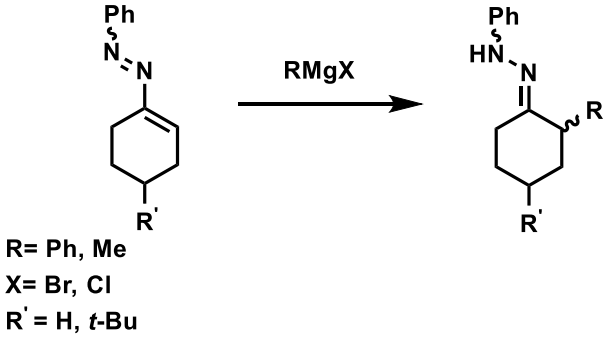
N-Tosyl α-epoxy hydrazones have shown wide utility in synthetic chemistry. Prominent example being the Eschenmoser-Tanabe fragmentation.[53,54] The fragmentation converts α-epoxy tosyl hydrazones to alkynes and acetylenic ketones or aldehydes in the presence of base (Scheme 1.19). A key intermediate in the proposed mechanism is β-hydroxy *N*-tosyl azoalkene which goes through rapid fragmentation, expelling nitrogen and sulfite anion. Beyond its use as a key intermediate within the Eschenmoser-Tanabe fragmentation, azoalkenes have been used as useful starting materials in Umpolung-like reactions for α-alkylation of ketones.[51,55]

Scheme 1.19 Eschenmoser-Tanabe Fragmentation



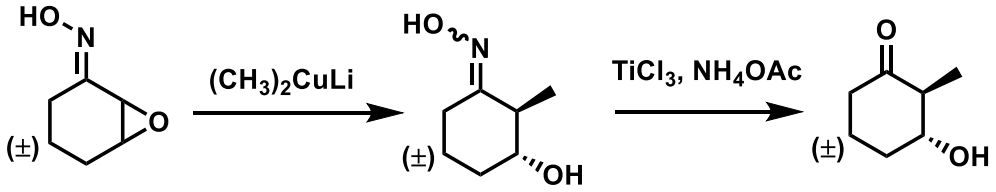
Bozzini pioneered α-alkylation of phenyl azoalkenes using Grignard reagents as alkylating agents (Scheme 1.20). He showed that both methyl and phenyl Grignard reagents can be used to alkylate the azoalkenes in good yields.[56] This system also works with bicyclic substances and on compounds functionalized at the γ-position.

Scheme 1.20 α-Alkylation of Phenyl-Azoalkenes



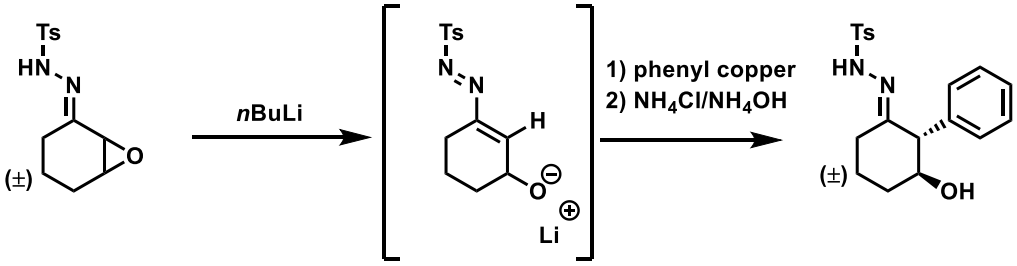
Corey in 1975 showed the utility of α-epoxy oximes using an aryl Gilman reagent to achieve diastereocontroled alkylation.[57] Corey does not explain how stereocontrol is achieved but it is possible that a Lewis acid (i.e. excess copper halide or lithium) is present within the reaction media. This would allow co-ordination of the alkoxide made *in situ* to the Lewis acid and prevent binding of the Gilman reagent formed from two equivalents of organolithium and copper halide to the alkoxide thus promoting opposite face attack (Scheme 1.21). Fuchs undertook a similar approach but α-epoxy tosyl hydrazone was used as a starting material, and phenyl copper instead of Gilman reagent was employed (Scheme 1.22).[58] In this transformation the desired *anti*-α-alkylated product is produced.

Scheme 1.21 Corey's α-Alkylation of Oximes Using Gilman Reagent



Another organometallic reagent that has been employed as a nucleophile in addition to azoalkenes is *n*-butyl lithium.[59] In a total synthesis of perhydrohistrionicotoxin, a nerve toxin found in poisonous frogs, a key transformation is the *in situ* azoalkene formation via ring opening of the *N*-tosy-α-epoxy hydrazone by LDA. The azoalkene is then alkylated with an excess of *n*-butyl lithium followed by silylation to form the *anti*- alkylated product which is then reacted further to form the desired natural product. The authors do not propose how diastereocontrol is achieved but based on the experimental data, the aggregation of the azoalkene and organolithium reagent might be directing the addition to the opposite face to afford the *anti*-isomer.

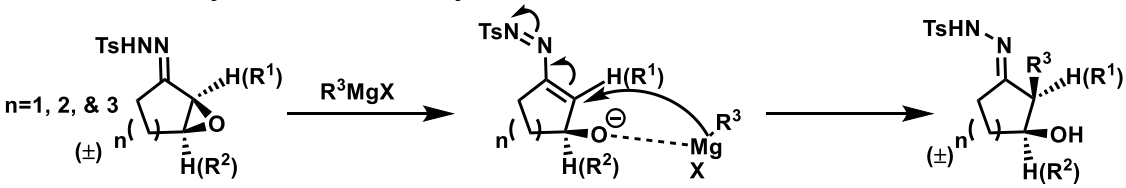
Scheme 1.22 Fuch's α-Alkylation of α-Epoxy Hydrazone Using Phenyl Copper



Coltart and coworkers developed a synthetic strategy towards *syn* alkylation of α-epoxy tosyl hydrazones using Grignard reagents (Scheme 1.23).[51] The rationale behind the synthetic strategy is that *in situ* formation of the azoalkene will be achieved by using two equivalents of the Grignard reagent. The first equivalent acts as a base, while the second equivalent of Grignard acts as the alkylating agent. Diasterecontrol is achieved by the magnesium of the Grignard reagent coordinating with the alkoxide of the azoalkene to allow same face addition of the alkylating group.[51] Using this synthetic strategy, the *syn* product is obtained in good to excellent yields. This strategy showcases the power of an Umpolung like approach as previously inaccessible functionality at the α-carbon can be added. Examples of such groups

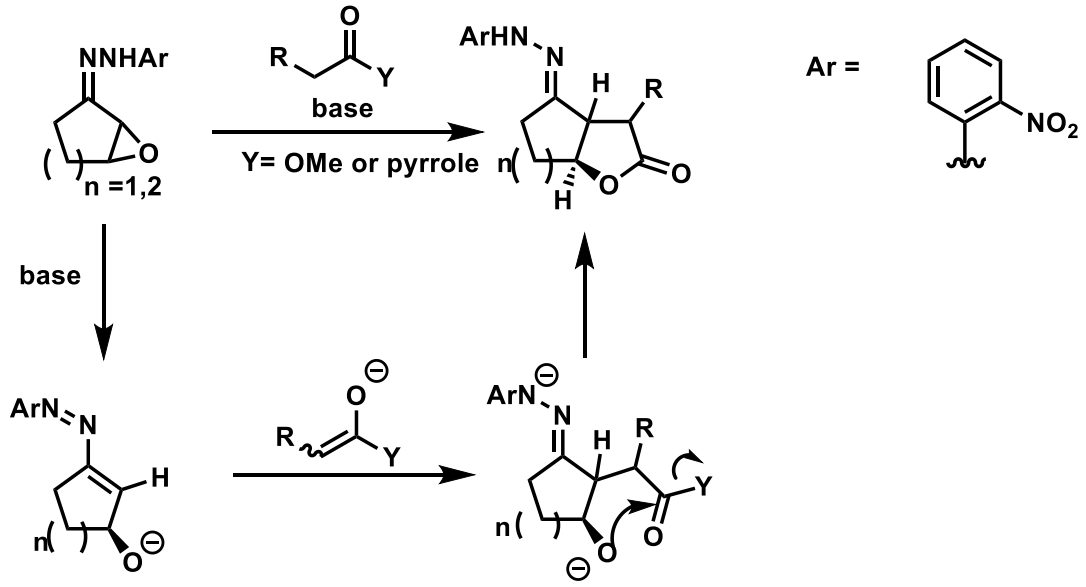
include phenyl, *t*-butyl, and vinyl moieties. Hydrazone removal is achieved with $CuCl_2$ and an acetone:1M phosphate buffer (pH 7) solution to regenerate the ketone. α,β-Functionalized ketones are a key scaffold used to prepare various biologically active compounds. Difficulties in their synthesis warrant the development of a straightforward method towards their formation.

Scheme 1.23 Coltart's *syn*-Selective α-Alkylation



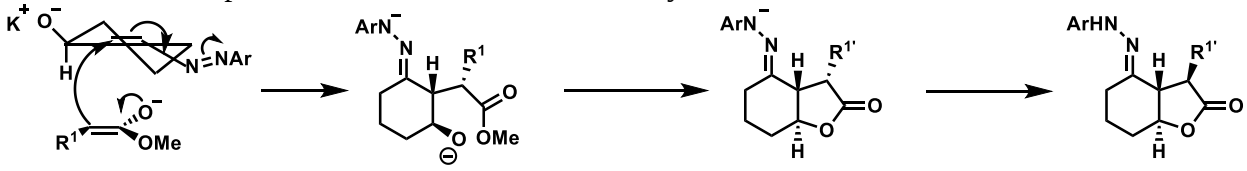
In addition to using organometallic reagents in reaction with azoalkenes, other soft nucleophiles have also been employed to achieve intermolecular alkylations. Coltart and co-workers developed a stereodivergent methodology towards both the *syn*- and *anti*- diasteromers of bicyclic β-lactones.[55] This is achieved by reacting α-epoxy 2-nitrophenyl hydrazone with an ester enolate formed *in situ* with KHMDS or LiHMDS to form the desired bicyclic fused rings (Scheme 1.24).

Scheme 1.24 Stereodivergent Ring Expansion Cascade Reaction of α-Epoxy-(2-Nitro)Phenyl Hydrazones and Ester Enolates

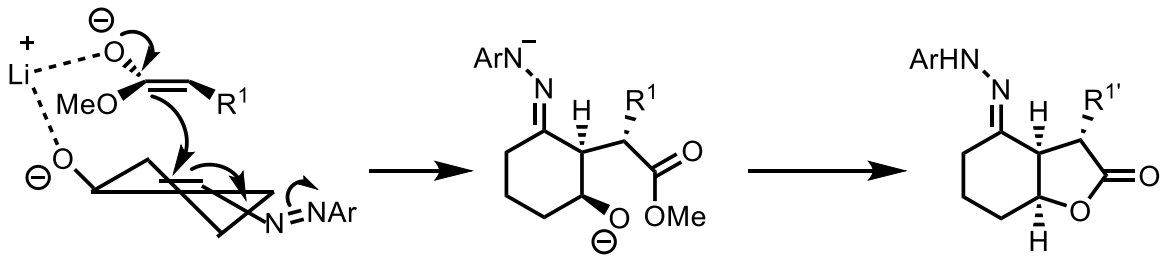


Stereocontrol is achieved by the binding of potassium or lithium *t*-butyl alkoxide (Schemes1.25 and 1.26). When using KHMDS, the potassium counterion is proposed to afford an open transition state where the ester enolate, with fixed geometry, attacks the azoalkene face opposite to the potassium alkoxide to establish the *anti*- configuration of the fused bicyclic lactone. Protonation and *O*- to *O*-acyl transfer produces the γ-lactone which may undergo epimerization at the β-position forming the thermodynamically favored *anti*- product.

Scheme 1.25 Proposed Mechanism for the anti- Bicyclic Fused Lactone Formation



Scheme 1.26 Proposed Mechanism for the syn-Bicyclic Fused Lactone Formation



To obtain the *syn*-lactone the researchers propose that an enolate of a defined geometry reacts diastereoselectively with the azoalkene in a closed transition state. This is achieved because lithium ion has a greater affinity for oxygen compared with potassium. This closed transition state promotes addition of the enolate to the same face of the alkoxy group thus establishing the *syn* configuration of the bicyclic fused lactone. Nitrogen protonation and *O*- to *O*-acyl transfer forms the γ-lactone which can subsequently undergo epimerization at the β-position to produce the more thermodynamically stable *syn*-lactone. Using enolates the Coltart group has produced both the *anti* and *syn* isomer from the same starting material. However, the corresponding transformations proved difficult to achieve when using Grignard reagents. In subsequent chapters, a methodology development for accessing the *anti*-α-alkylated product from an azoalkene will be discussed. We will also discuss how soft enolization was used to form 1,3-diketones and β-keto thioesters in a convenient one pot fashion using crude acyl chloride reagents.

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CHAPTER 2

PREPARATION OF 1,3-DICARBONYL MOTIF VIA SOFT ENOLIZATION

2.1 Introduction

1,3-Diketones and β-keto thioesters are important compounds in synthetic organic chemistry.[1] Hard enolization is predominantly used to form these structural motifs. Notable examples of enolization strategies towards 1,3-diketone or β-keto thioester synthesis include pre-formation of a silyl enol ethers[2,3] and lithiated enolates[4] by using LiHMDS base. Rathke's preparation of 1,3-diketones uses a tertiary amine in addition to sodium iodide and trimethylsilane to form the desired enolate.[2,5] Whilst effective, these approaches give low yields of the desired 1,3-dicarbonyl product. Many acylating agents can be used as previously discussed in Chapter 1 but the most common acylating reagents used for 1,3-dicarbonyl formation under soft enolization conditions include acyl pyrazoles,[6] acyl chlorides,[2-4] and acyl triazoles.[7,9,10]

Despite the importance of 1,3-diketones and β-keto thioesters, their synthesis using conventional hard enolization can be problematic. Hard enolization methodology can suffer from poor selectivity in deprotonation if there is acidic functionality elsewhere in the reactant, *O*-acylation, bis-acylation, and use of operationally laborious steps. Soft enolization is useful alternative as it alleviates many of the issues inherent to hard enolization. This is possible as the enolate formation occurs under milder reaction conditions where a weak base is used in conjunction with Lewis acid to effect deprotonation reversibly. The Lewis acid is required as it binds to the carbonyl oxygen of the enolate precursor to polarize it, thus increasing the acidity of the α-proton. The increased acidity of the α-proton makes it susceptible to deprotonation with a weak base, which would not be possible without the Lewis acid.[9]

The Coltart group has developed a program around the formation of various biologically important scaffolds using soft enolization conditions.[10-15] Notable examples are the syntheses

of 1,3-diketones and β-keto thioesters using *N*-acybenzotriazoles or *O*-Pfp esters as acylating components and ketones or thioesters as the enolate precursors.[9] While acyl triazoles and fluorinated esters can be effective acylating agents, they are not ideal from a cost or atom economy perspective. Direct acylation of carboxylic acids is still elusive; however, acyl chlorides would be convenient to use as well. Use of acid chlorides as acylating agents is well known, as they are very reactive, and either commercially available, or easily prepared from carboxylic acids. A previous attempt of using acyl chlorides under soft enolization conditions was reported by Coltart and co-workers.[9] Unfortunately, when using *n*-valeryl chloride further acylation of the 1,3-diketone was observed due to the presence of several acidic protons. Upon revisiting the project, it became apparent that the use of acid chlorides would still be useful even if they did not function as well as *N*-acylbenotriazole and *O*-Pfp ester reagents. Their ease of accessibility and atom economy would justify their use in many synthetic applications. Another appealing aspect was using crude acyl chloride in the carbon-carbon bond forming step as this allows for a one pot synthetic reaction of using carboxylic acids towards 1,3-diketone and β-keto thioester formation. Using crude acylating agent to prepare the desired 1,3-dicarbonyl with good yields would be difficult if not impossible under hard enolization conditions.

The use of crude acyl chloride to obtain high yields of 1,3-diketones and β-keto thioesters is possible under soft enolization conditions as the enolate formation is under equilibrium conditions. This is possible as the enolate exists in the presents of a reactant bearing acidic functionality. If a small amount of enolate is present, reacting with crude acyl chloride will be energetically driven to a new carbon-carbon bond formation. As discussed in Chapter 1, hard enolization possesses many problems towards effective 1,3-dicarbonyl synthesis. In

Chapter 2 we will discuss the development of a synthetic method for preparation of 1,3-diketones and β-keto thioesters with good yields without *O* – or bis-acylation.

2.2 Results

2.2.1 Selecting a Lewis Acid

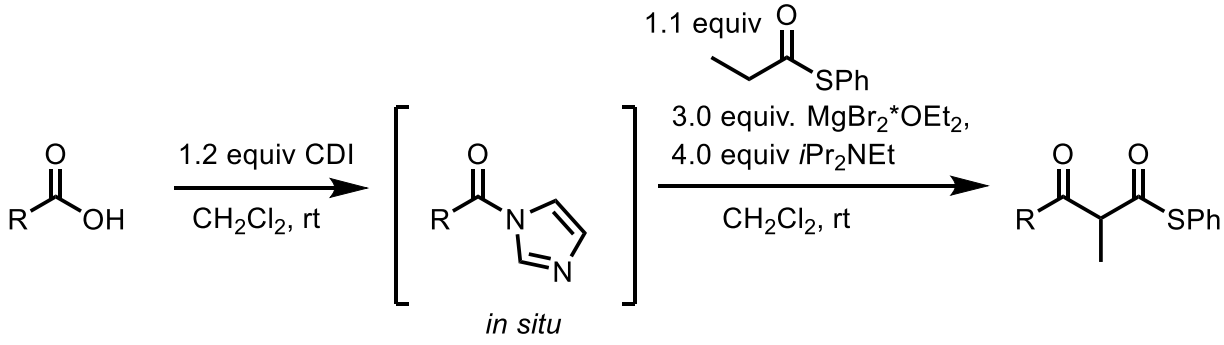
There is a vast number of commercially available Lewis acids, and the challenge becomes selecting one that allows good enolate formation under desired reaction conditions. A good Lewis acid for soft enolization must be soluble, bind to the carbonyl of the enolate precursor, and facilitate minimal side reactions. The most important attribute of the Lewis acid is its to coordinate to the carbonyl. Without binding of the Lewis acid to the enolate precursor, acidity of the α proton is not sufficient to allow direct enolate formation with a weak base. Based on the reactivity screening performed by Coltart,[17] $MgBr_2$*OEt_2 and *i*Pr_2NEt in THF combination was selected due to producing the highest conversion to the 1,3-diketone products. Determination of the conversion was determined by integration ^{1}H-NMR signals of the α-proton against an internal standard.

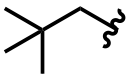
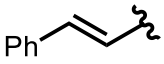
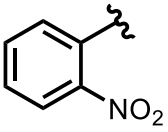
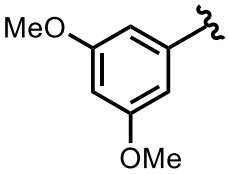
2.2.2 Using Acylimidazoles as Acylating Agents

Previous work by Coltart used *N*-acylbenzotriazole and ketones to synthesize 1,3-diketones.[9] However, this method is limited by relatively expensive reagents and requirement to purify the acylating agent before use. We conceived a streamlined methodology where no further purification of the acylating agent is required and thus reduce expense of this reaction by using *in situ* formation of acylimidazole acylating agent.[17] The synthesis of this acylating agent can be achieved by reacting 1,1'-carbonylimidazole (CDI) with carboxylic acids (Table

2.1). From a practical point of view, using acylimidazole in a direct Claisen reaction is desirable because no further purification of the active acyl component is needed. Using an acylimidazole intermediate as an electrophile and *S*-phenylthiopropionate enolate precursor produced low yield of β-keto thioester (Table 2.1). The product was obtained with neopentyl derivative, but only 35% yield was obtained (**entry 1**). Since our use of acylimidazoles did not give favorable results, we sought to use acid chlorides as an acylating agents under soft enolization conditions.

Table 2.1 Reaction Screen of Acylimidazole with S-phenylthiopropionate

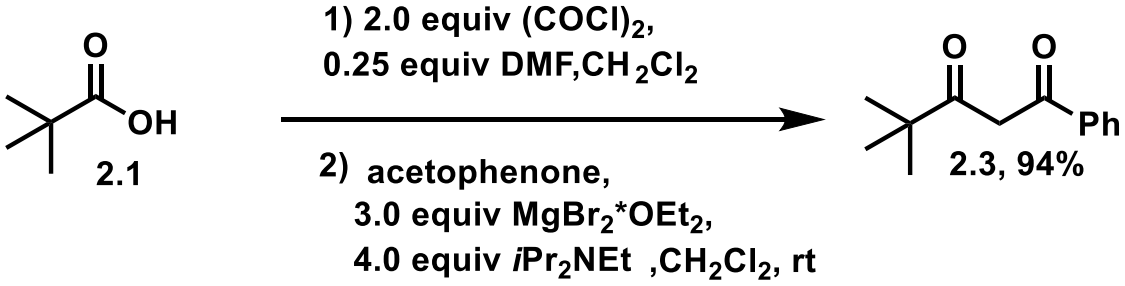


Entry	R	%Yield
1		35%
2		0
3		0
4		7%

2.2.3 Synthesis of 1,3-Diketones by Employing Acid Chlorides

Synthetic methodology for preparation of 1,3-diketones under soft enolization conditions using a magnesium based Lewis acid was previously developed by Ravn and co-workers.[16] However, they did not show its utility in formation of β-keto thioesters nor dd they exploit the thermodynamic conditions of enolate formation. Taking this into consideration, a synthetic methodology was developed where crude acyl chloride could be coupled with ketones or thioesters to form the desired 1,3-dicarbonyl products. Crude acyl chloride was formed by treating a solution of 2-methylpropionic acid **2.1** in DMF and CH_2Cl_2 with oxalyl chloride (Scheme 2.1). The solvent was then removed under reduced pressure resulting in an oil that was dissolved in CH_2Cl_2, combined with $MgBr_2$*OEt_2, *i*-Pr_2NEt, and acetophenone. These mild reaction conditions lead to the formation of the desired product **2.3** in 94% yield. The use of acetophenone as an enolate precursor was tested further using a variety of carboxylic acids. The yields of the 1,3-diketones shown in Tables 2.2 and 2.3 range from 68% to 94%, showing that the reaction conditions are robust and can handle a wide range carboxylic acid substrates.

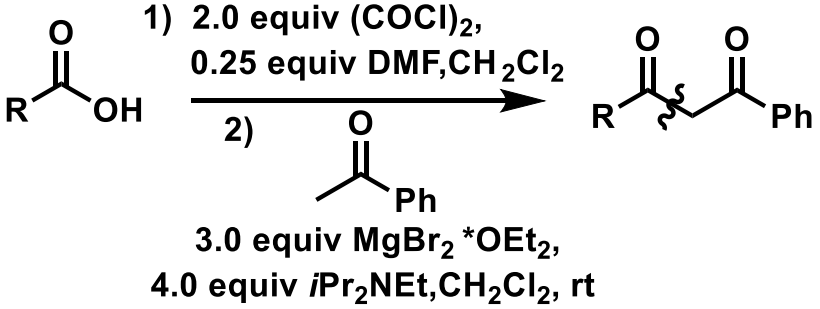
Scheme 2.1 Synthesis of 4,4-Dimethyl-1-Phenyl-Pentane-1,3-Dione

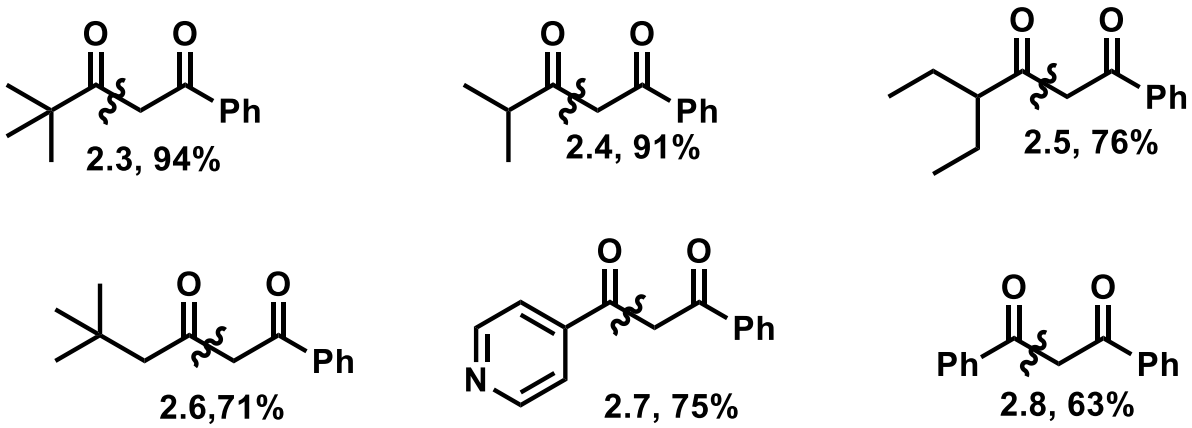


The synthetic conditions shown in Table 2.2. work for molecules bearing a tertiary substituent such as compound **2.3** at 94% as well as with an enolizable neopentyl-derived compound **2.6** at 71% yield. No bis-acylation of enolizable products was observed for **2.4** and

2.5; the desired 1,3-diketone was isolated in 91% and 76% yields, respectively. These conditions are also compatible with aryl and heterocyclic moieties such as **2.7** (75% yield) and the phenyl derived **2.8** (63% yield).

Table 2.2 Preparation of Acyclic 1,3-Diketones via Crude Acyl Chloride

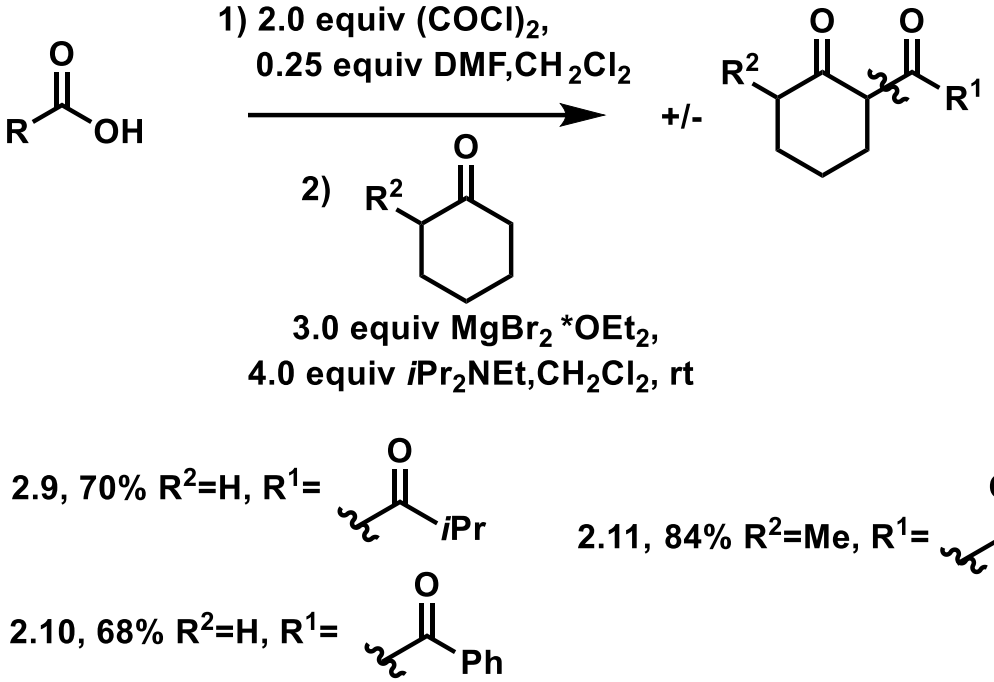




Use of crude acyl chlorides is compatible when using different ketones also other than acetophenone. In Scheme 2.2, different cyclic ketones react well with crude acyl chlorides to provide good yields of the desired 1,3-diketones. Again, the reaction conditions are tolerant to reagents bearing enolizable protons. Cyclohexane reacted with crude *iso*-butyryl chloride to give **2.9** in 70% with no observed bis-acylation. The reaction conditions also allowed monoacylation of cyclohexanone using crude benzoyl chloride to give **2.10** in 68% yield.

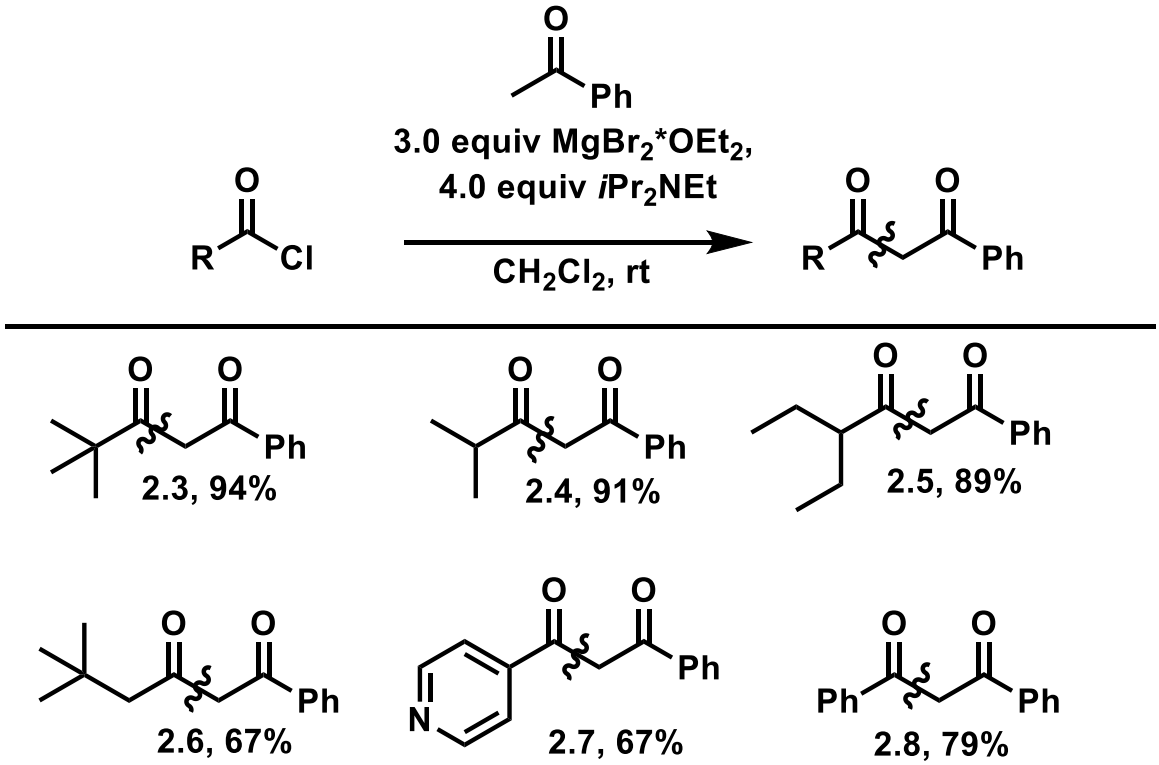
Interestingly, the reaction also showed excellent regioselectivity as the less sterically hindered side of compound **2.11** was acylated in a good yield of 84%.

Scheme 2.2 Preparation of Cyclic 1,3-Diketones via Crude Acyl Chloride



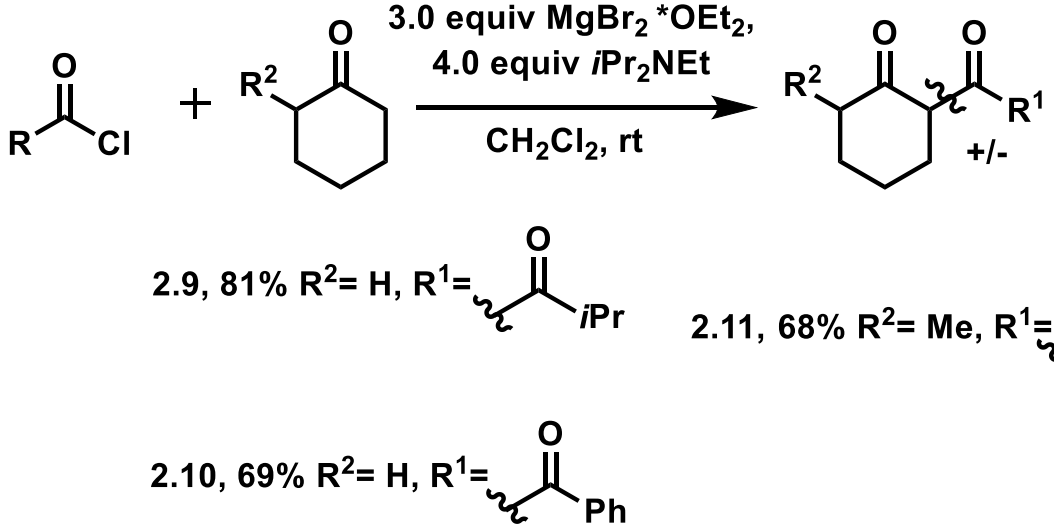
Comparable yields were observed when using commercially available acyl chloride as the acylating agents (Table 2.3). Under our approach, *t*-butyl substituted compound **2.3** was formed in 94% and β-substituted compound **2.6** bearing an enolizable neopentyl group, can be prepared in 71% yield. To our delight, the reaction did not result in bis-acylation of compounds bearing enolizable protons such as those in products **2.4** and **2.5**; the desired 1,3-diketone was isolated in 91% and 76% yields, respectively. These conditions are also compatible with aryl and heterocyclic functional groups such as the pyridyl-substituted **2.7** (75% yield) and the phenyl-substituted **2.8** (63% yield).

Table 2.3 Preparation of Acyclic 1,3-Diketones from Commercial Acyl Chloride



In using commercially available acid chlorides paired with cyclic enolizable ketones (Scheme 2.3), our reaction conditions gave similar yields to those shown in Table 2.1 and Scheme 2.2. In reacting cyclohexane with crude *iso*-butyryl chloride product **2.9** was obtained in 81% yield with no observed bis-acylation at other acidic sites. This is higher than the reported 70% using crude acyl chloride (Scheme 2.2). The reaction conditions also allowed monoacylation of cyclohexanone using benzoyl chloride to give **2.10** in 68% yield, which is similar result to one obtained with crude acyl chloride. Comparable regioselectivity and yield were observed when using 2-methyl cyclohexanone to form **2.11** in 68% yield.

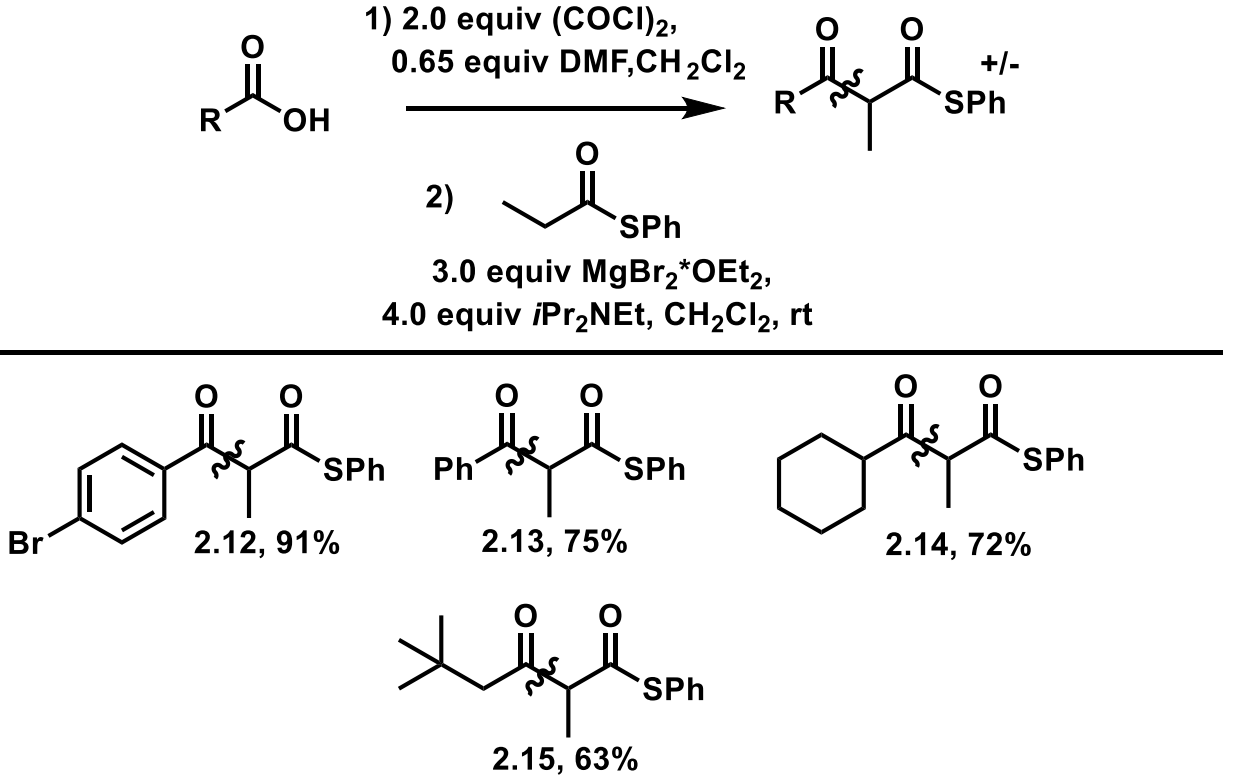
Scheme 2.3 Preparation of 1,3-Diketones via Commercial Acyl Chlorides



2.2.4 Synthesis of β-Keto Thioesters

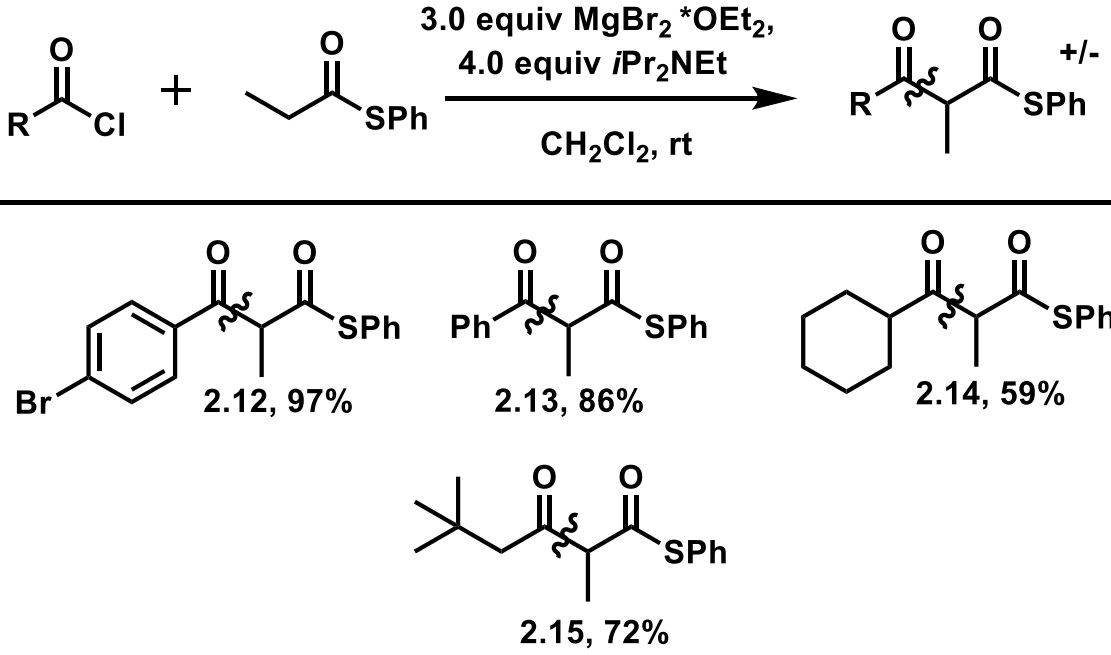
As mentioned in Chapter 1, the Coltart group had previously reported acylation of thioesters using *N*-acylbenotriazoles in the presence of $MgBr_2$*OEt_2 and Hünig's base to give β-keto thioesters.[11] Given that the synthesis of 1,3-diketones using crude acyl chlorides gave comparable and at times improved yields to commercially available acid chlorides, it was considered worth applying this approach to the synthesis of β-keto thioesters. The reaction conditions are the same as shown previously but using *S*-phenylthiopropionate as the enolate precursor. Various crude acid chlorides produced the desired β-keto ester in yields ranging from 63% to 97% from crude acyl chlorides (Table 2.4). This result was found to be comparable to reaction conditions using commercially sourced acid chlorides (Table 2.5). This further validates that soft enolization conditions can be used in a "one-pot" fashion to synthesize 1,3-diketones and β-keto thioesters in good to excellent yields.

Table 2.4 Preparation of β-Keto Thioesters Using Crude Acyl Chlorides



Crude acyl chlorides bearing both enolizable and non-enolizable substituents were used to obtain desired products. The reaction conditions are tolerant to aryl functionality. 4-Bromobenzoyl chloride gave the desired compound in 91% yield. Use of benzoyl chloride gave **2.13** in 75% yield. The reaction conditions are tolerant to enolizable moieties such as cyclohexanylcarbonyl chloride, yielding 72% of **2.14**. Use of sterically hindered enolizable neo-pentyl acetyl chloride also produced the desired product **2.15** in 63% yield. No bis-acylated products were observed.

Table 2.5 Preparation of Cyclic β-Keto Thioesters Using Commercial Acyl Chlorides



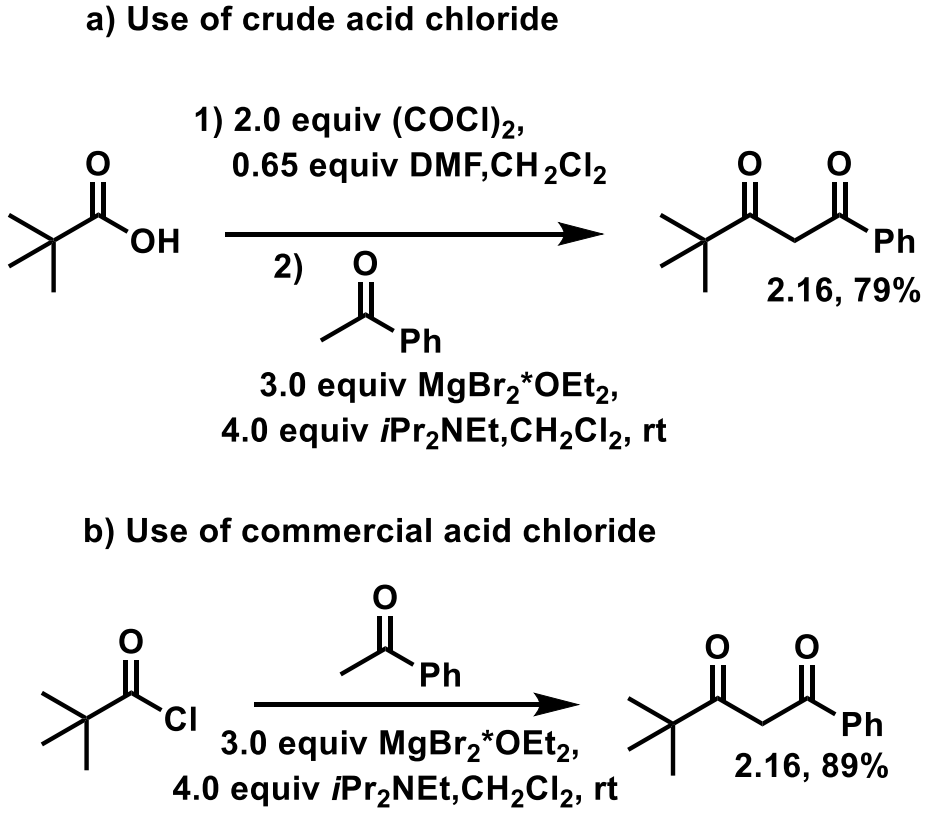
Comparable yields to those shown in Table 2.4 were obtained when using commercially available acyl chlorides (Table 2.5). These experiments were performed to compare the reactivity of using crude acyl chloride under soft enolization conditions. Overall, yielding with commercial acyl chlorides matched results shown for crude acyl chlorides (Table 2.4). If crude acyl chlorides were used, products **2.12** and **2.13** gave the desired β-keto thioesters in 97% and 86% yields, nearly identical to yields obtained with commercially available starting material (Table 2.4, 91% and 75% yields). An enolizable commercially available cyclohexanylcarbonyl chloride gave the desired dicarbonyl, **2.14**, in 59% yield. However, this is lower yield than using crude acyl chloride (Table 2.4). For sterically hindered enolizable acyl chlorides such as 3,3 dimethylbutanoyl chloride the reaction conditions proved ideal as 2.15 was obtained in 72% yield. This result matches the 68% yield for the same product formed using crude acyl chloride. Overall, soft enolization conditions show excellent chemoselectivity as both *O*- and bis-

acylation products were formed. We also obtained good to excellent yields of the desired 1,3-dicarbonyl products, demonstrating that these reaction conditions can handle a wide range of substrates.

2.2.5 Scalability

We were able to obtain consistently good yields when forming diketone motifs under the newly developed reaction conditions. Consequently, we investigated the scalability of the reaction next. Abbot Laboratories have already used soft enolization procedures developed by the Coltart lab towards large scale synthesis of DGAT-1 inhibitors.[16] The synthesis of diketone **2.3** was performed by first forming the crude acyl chloride in a 5.0 g scale (Scheme 2.4) by reacting a solution of pivalic acid in DMF and CH_2Cl_2 with 2.0 equivalents of oxalyl chloride. After stirring for 12 h, the solvent was removed resulting in a residue which was dissolved in CH_2Cl_2, followed by addition of $MgBr_2$*OEt_2, *i*Pr_2NEt, and then acetophenone. The desired product **2.3** was isolated in 79% yield (Table 2.2). The reaction was repeated by using commercially available acid chloride which gave similar 89% yield of **2.3** (Scheme 2.3). This transformation using the crude acyl chloride shows synthetic utility of the approach on a large reaction scale.

Scheme 2.4 Scalability of Soft Enolization Method

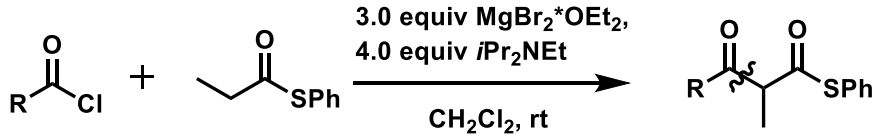


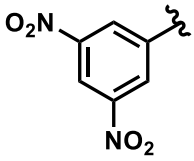
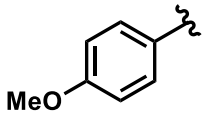
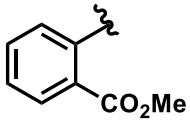
2.3 Discussion

Investigating the reactivity trends of acid chlorides in reaction with *S*-phenyl thiopropionoate under soft enolization conditions shows that there are no distinct electronic or steric effects if using alkyl or aromatic coupling partners. For the formation of 1,3-diketones, cyclic alkyl containing species reacted well under soft enolization conditions as shown above. However, for β-keto thioesters, problems arise when the aromatic acyl chlorides contain either an electron donating or withdrawing component at different substituted positions. In some cases, desired products were not formed (Table 2.6). The only exception was the *p*-bromo phenyl substituted acid chloride, which gave the diketone in 91% and 97% yields in using crude or commercial grade acyl chlorides, respectively (Tables 2.4 and 2.5). A proposed rationale to

the poor reactivity of some of the acyl chlorides could be their binding ability to Lewis acid thus impeding the reaction. Instead, binding/interacting with the acylating agent must occur on Lewis basic functional groups.

Table 2.6 Failed Reactivity of Some Acyl Chlorides

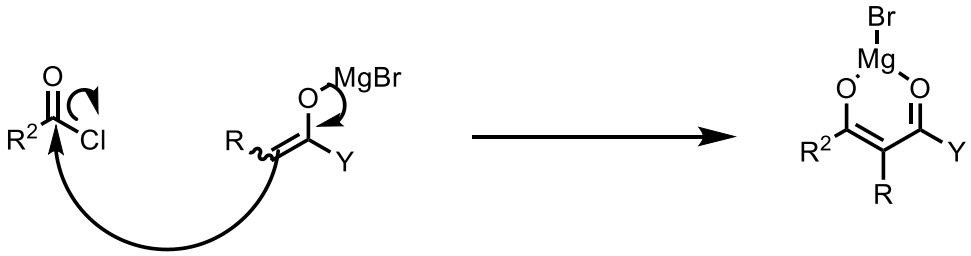


Entry	R	Yield
5		0%
6		0%
7		0%

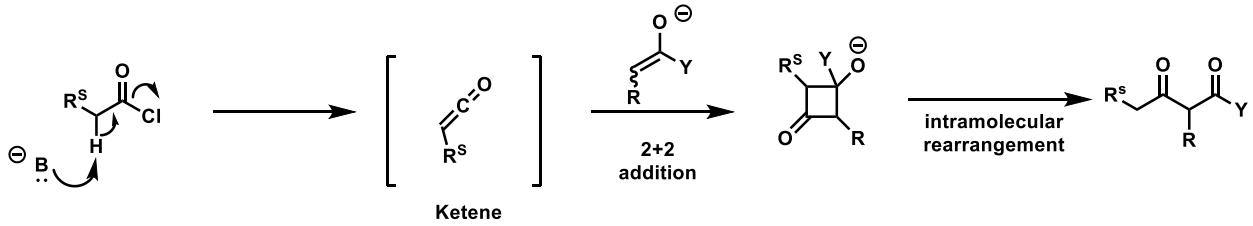
Excellent chemoselectivity was achieved as no *O*-acylated or bis-acylated products were obtained. In terms of mechanistic understanding, there are two possibilities based on the type of acyl chloride used. For acyl chlorides not bearing an α-proton, reactions most likely proceed via an S_N 2-like mechanism (Scheme 2.5).[19] The enolate attacks the acid chloride to form the desired 1,3-dicarbonyl species. For acyl chlorides bearing an α-proton, the mechanism is less clear. Such acid chlorides mat react via ketene intermediate in the presence of a tertiary amine (Scheme 2.6).[17] The ketene can then react with the enolate in a formal 2+2 addition

forming a cyclic ester or thioester followed by rapid fragmentation to form the desired 1,3-dicarbonyl. A mechanistic study was not carried out to confirm or reject this hypothesis, however, based on analogous studies, we believe that for acyl chlorides bearing an enolizable α-proton ketene formation, while less likely, cannot be ruled out.[20]

Scheme 2.5 S_N2-like Reaction of Acyl Chlorides



Scheme 2.6 Potential Formation of Ketene Intermediate During Deprotonation of Acyl Chloride



2.4 Conclusions

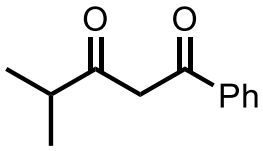
In conclusion, under soft enolization conditions, the acylation of ketones and thioesters using crude or commercial grade acyl chlorides can be used to synthesize 1,3-diketones and β-keto thioesters, respectively. Due to the general importance of the 1,3-dicarbonyl motif, we have created an efficient and operationally simple approach that may find wide applicability in synthetic chemistry.

2.5 Experimental Section

All reactions were carried out under dried solvents under a slight static pressure of Ar (prepurified quality) that had been passed through a 5 x 20 cm column of Drierite. Glassware was dried in an oven at 120 ^{o}C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Dry solvents were obtained using an Innovative Technologies solvent purification system. Commercial grade solvents were used for routine purposes without further purification. Amines were distilled from CaH_2 under N_2 atmosphere prior to use. Column chromatography was performed on 230-400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometers at ambient temperature. High-resolution mass spectrometry was performed using an Agilent Technologies 6530 Accurate Mass Q-Tof LC-MS for electrospray ionization (ESI) or a Micromass Autospec Ultima for chemical ionization (CI).

2.5.2 Synthesis and Characterization

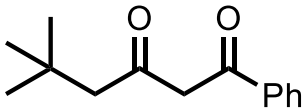
General Synthesis of 1,3-Diketones from Carboxylic Acids



4-Methyl-1-phenyl-pentane-1,3-dione (2.4)

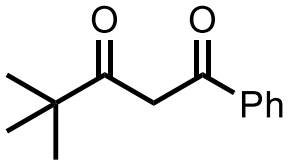
Dimethylformamide (0.23 mL, 2.88 mmol) was added to a stirred solution of 2-methylpropionic acid (2.0 mL, 22.2 mmol), oxalyl chloride (5.7 mL, 66.5 mmol), and CH_2Cl_2 (50 mL) under Ar atmosphere. The solution was stirred for 12 h and then evaporated under reduced pressure to

give a mixture of a yellow oil and dark-brown residue. In a separate flask, $MgBr_2$*OEt_2 (0.71 g, 2.80 mmol) was added to a stirred solution of acetophenone (0.13 mL, 0.915 mmol) and the above-generated yellow oil(0.2 mL; ~1.9 mmol) in CH_2Cl_2 (3 mL) under Ar atmosphere, and the resulting mixture was stirred for 15 min. Diisopropylethyl amine (0.636 mL, 3.66 mmol) was then added dropwise over ~1 min, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and the mixture was stirred for 12 h. The reaction was quenched with 10% $HCl_{(aq)}$ (4 mL), and the resulting mixture was partitioned between CH_2Cl_2 (15 mL) and water (8 mL). The aqueous phase was washed with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (2 × 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.4** as a red oil (0.164 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99−7.88 (m, 2H), 7.53−7.41 (m, 3H), 6.10 (s, 1H), 4.10 (s, 1H), 2.70−2.58 (m, 1H), 1.20 (d, J = 9.2 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 201.3, 183.9, 135.3, 132.3, 128.7, 127.1, 94.3, 37.6, 19.5.



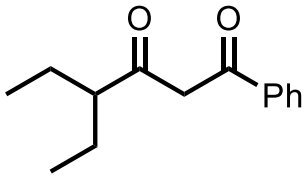
1-Phenyl-5,5-dimethylhexane-1,3-dione (2.6)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 CH_2Cl_2–hexanes (v/v) gave **2.6** as a red oil (0.355 g, 71%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, J = 6.8 Hz, 2H), 7.55–7.42 (m, 3H), 6.13 (s, 1H), 2.28 (s, 2H) 1.06 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 193.9, 185.4, 135.6, 132.4, 128.7, 127.2, 98.3, 52.4, 32.1, 30.1.



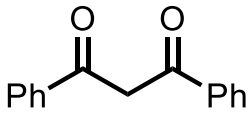
4,4-Dimethyl-1-phenyl-pentane-1,3-dione (2.3)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 10:90 CH_2Cl_2–hexanes (v/v) gave **2.3** as a a red oil (0.165 g, 94%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.53–7.49 (m, 1H), 7.47–7.43 (m, 2H), 6.31 (s, 1H), 1.25 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$,100 MHz): δ 202.9, 184.7, 135.6, 132.3, 128.7, 127.1, 92.2, 39.9, 27.5.



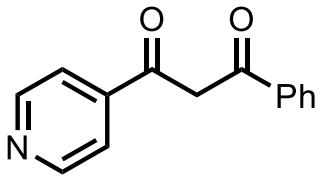
4-Ethyl-1-phenylhexane-1,3-dione (2.5)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.5** as a red oil (0.142 g, 76%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99−7.88 (m, 2H), 7.62−7.43 (m, 3H), 6.1 (s, 1H), 4.1 (s, 8H), 2.20−2.12 (m, 1H), 1.72−1.51 (m, 4H), 0.9 (t, *J* = 7.4 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 199.4, 184.4, 135.4, 132.3, 128.7, 127.2, 96.5, 52.7, 25.7, 12.1.



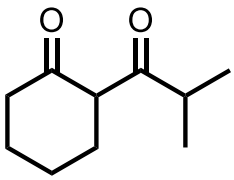
1,3-Diphenyl-1,3-propanedione (2.8)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.8** as a yellow solid (0.116 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.59–7.48 (m, 4H), 6.87 (s, 1H), 3.46 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): 202.5, 184.3, 134.8, 132.8, 129.1, 128.8, 92.1, 40.1, 28.1.



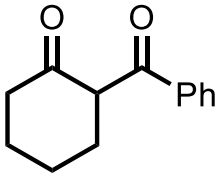
1-Phenyl-3-(4-pyridyl)-1,3-propanedione (2.7)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.7** as a yellow solid (0.219 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.21 (s, 1H), 8.78 (d, *J* = 3.6 Hz, 1H), 8.39–8.37 (m, 1H), 7.99 (d, *J* = 3.1 Hz, 2H), 7.6–7.48 (m, 5H), 6.89 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 186.4, 183.4, 152.9, 148.6, 134.7, 133.0, 128.9, 127.4, 123.7, 93.6.



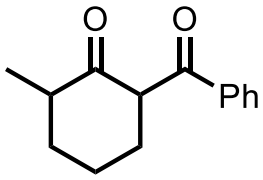
2-(2-Methylpropanoyl)cyclohexanone (2.9)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.9** as a yellow solid (0.227 g, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.91−2.80 (m, 1H), 2.41−2.33 (m, 4H), 2.72−1.67 (m, 4H), 1.07 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 205.5, 183.1, 105.7, 33.3, 31.4, 23.7, 23.1, 21.7, 18.8.



2-Benzoylcyclohexanone (2.10)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.10** as a yellow solid (0.133 g, 68%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, *J* = 7.2 Hz, 1H), 7.61–7.58 (m, 2H), 7.54–7.45 (m, 3H), 4.4 (dd, *J* = 3.5 Hz, 1H), 3.56−3.47 (m, 1H), 2.51(t, *J* = 6.1 Hz, 2H), 2.41 (t, *J* = 6.2 Hz, 2H), 2.3–2.2 (m, 1H), 2.11−1.99 (m, 2H), 1.91–1.56 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 191.2, 189.6, 130.5, 128.7, 128.6, 128.2, 127.7, 59.3, 42.5, 26.6, 23.5, 21.9.

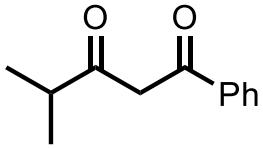


2-Benzoyl-6-methyl-cyclohexanone (2.11)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95, EtOAc–hexanes (v/v) gave **2.99** as a colorless solid (0.150 g, 84%). ^{1}H NMR ($CDCl_3$, 400

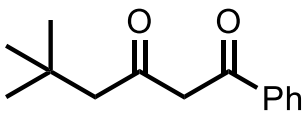
MHz): δ 7.57–7.50 (m, 2H), 7.46–7.39 (m, 3H), 4.45 (dd, *J* = 3.2 Hz, 1H), 2.56−2.36 (m, 2H), 2.11–1.89 (m, 2H), 1.75–1.67 (m, 1H), 1.54–1.39 (m, 2H), 1.26 (d, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 210.31, 198.1, 136.8, 132.5, 128.8, 128.7, 58.3, 46.2, 36.4, 30.1, 24.3, 14.5.

General Synthesis of 1,3-Diketones from Pure Acyl Chlorides



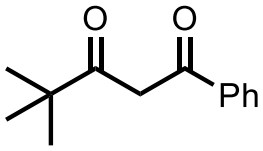
4-Methyl-1-phenyl-pentane-1,3-dione (2.4)

Solid $MgBr_2 \cdot OEt_2$ (1.38 g, 5.35 mmol) was added to a stirred solution of acetophenone (0.20 mL, 1.95 mmol), 2,2'-dimethyl butyl chloride (0.20 mL, 2.19 mmol), and CH_2Cl_2 (7 mL) under Ar atmosphere, and the resulting mixture was stirred for 15 min. Di-isoproylethyl amine *i*-Pr_2NEt (1.16 mL, 7.13 mmol) was added to the solution, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and reaction mixture was stirred for 12 h. The reaction mixture was then quenched with 10% $HCl_{(aq)}$ (4 mL), and the resulting mixture was partitioned between CH_2Cl_2 (15 mL) and water (8 mL). The aqueous phase was washed with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (2 × 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.4** as a red oil (0.299 g, 91%). Spectroscopic data are identical to those given above.



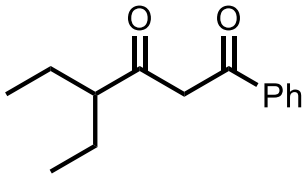
1-Phenyl-5,5-dimethylhexane-1,3-dione (2.6)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 CH_2Cl_2–hexanes (v/v) gave **2.6** as a red oil (0.125 g, 67%). Spectroscopic data are identical to those given above.



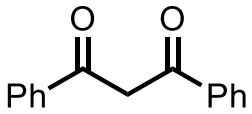
4,4-Dimethyl-1-phenyl-pentane-1,3-dione (2.3)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 10:90 CH_2Cl_2–hexanes (v/v) gave **2.3** as a red oil (0.330 g, 94%). Spectroscopic data are identical to those given above.



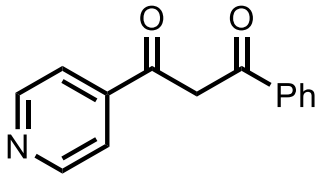
4-Ethyl-1-phenylhexane-1,3-dione (2.5)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.5** as a red oil (0.326 g, 89%). Spectroscopic data are identical to those given above.



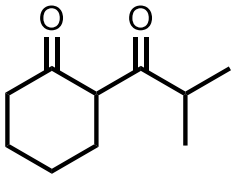
1,3-Diphenyl-1,3-propanedione (2.8)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.8** as a yellow solid (0.301 g, 79%). Spectroscopic data are identical to those given above.



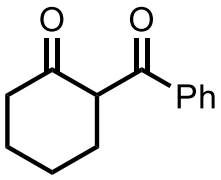
1-Phenyl-3-(4-pyridyl)-1,3-propanedione (2.7)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.7** as a yellow solid (0.086 g, 67%). Spectroscopic data are identical to those given above.



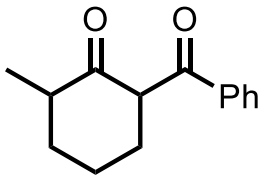
2-(2-Methylpropanoyl)cyclohexanone (2.9)

Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.9** as a yellow solid (0.169 g, 81%). Spectroscopic data are identical to those given above.



2-Benzoylcyclohexanone (2.10)

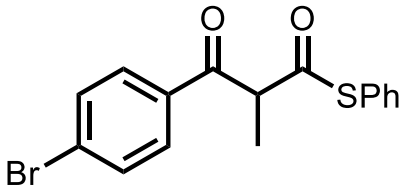
Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.10** as a yellow solid (0.270 g, 69%). Spectroscopic data are identical to those given above.



2-Benzoyl-6-methyl-cyclohexanone (2.11)

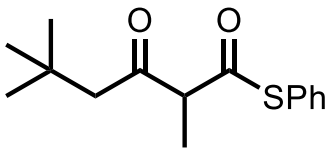
Procedure was performed as with 2.4 above. Flash chromatography over silica gel using 5:95, EtOAc–hexanes (v/v) gave **2.11** as a colorless solid (0.356 g, 68%). Spectroscopic data are identical to those given above.

General synthesis of β-Keto Thioesters from Carboxylic Acids



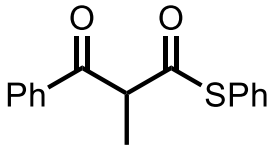
***S*-Phenyl 1-(4-bromophenyl)-3-propane-1,3-dione (2.12)**

Dimethylformamide (0.11 mL, 1.43 mmol) was added to a stirred solution of 4-bromobenzoic acid (2.50 g, 11.4 mmol), oxalyl chloride (3.0 mL, 34.9 mmol), and CH_2Cl_2 (80 mL) under Ar atmosphere. The solution was stirred for 12 h and then evaporated under reduced pressure to give a light-yellow solid. In a separate flask, $MgBr_2 \cdot OEt_2$ (1.0 g, 3.90 mmol) was added to a stirred solution of *S*-phenyl propanethioate (0.20 mL, 1.30 mmol) and the above-generated yellow solid (0.36 g; ~2.6 mmol) in CH_2Cl_2 (4 mL) under Ar atmosphere. The resulting mixture was stirred for 15 min. Di-isopropylethyl amine (0.90 mL, 5.20 mmol) was added dropwise over ~1 min, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and the mixture was stirred for 12 h. The reaction was quenched with 10% $HCl_{(aq)}$ (4 mL), and the resulting mixture was partitioned between CH_2Cl_2 (15 mL) and water (8 mL). The aqueous phase was washed with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (2 × 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.12** as a white solid (0.414 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85–7.83 (m, 2H), 7.68–7.6 (m, 2H), 7.39–7.25 (m, 5H), 4.66 (q, J = 6.8 Hz, 1H), 2.16 (s, 1H), 1.59 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 194.9, 193.8, 134.6, 130.4, 129.9, 129.5, 129.2, 126.6, 123.3, 56.4, 14.8. HRMS ESI-MS *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}BrO_2S$ 348.9892, found 348.9900 and 350.9882.



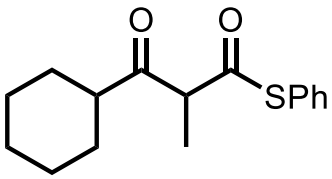
_S_-Phenyl 2,5,5-trimethyl-3-oxohexanethioate (2.15)

Procedure was performed as with 2.12 above. Flash chromatography over silica gel using 30:70 CH_2Cl_2–hexanes (v/v) gave **2.15** as a yellow oil (0.207 g, 63%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.94−7.82 (m, 2H), 7.58−7.41 (m, 3H), 6.32 (s, 1H), 5.23 (s, 1H), 1.31 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 203.8, 184.9, 136.5, 132.3, 129.4, 128.3, 92.4, 40.1, 28.2.



***S*-Phenyl 2-methyl-3-oxo-3-phenylpropanethioate (2.13)**

Procedure was performed as with 2.12 above. Flash chromatography over silica gel using 20:80 CH_2Cl_2–hexanes (v/v) gave **2.13** as a yellow oil (0.115 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (s, 1H), 8.02 (d, *J* = 1.2 Hz, 1H), 7.62–7.56 (m, 1H), 7.52–7.48 (m, 2H), 7.39–7.34 (m, 5H), 4.71 (q, *J* = 7.2 Hz, 1H), 1.61 (d, *J* = 6.8 Hz, 3H), 2.1 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 195.01, 194.8, 135.9, 134.6, 133.8, 129.8, 129.4, 128.96, 128.91, 126.9, 56.3, 14.9.

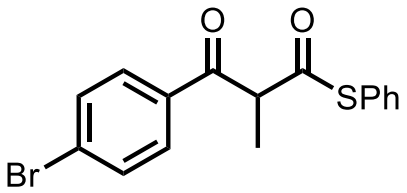


***S*-Phenyl 3-cyclohexyl-2-methyl-3-oxopropanethioate (2.14)**

Procedure was performed as with 2.12 above. Flash chromatography over silica gel using 20:80 CH_2Cl_2–hexanes (v/v) gave **2.14** as a red oil (0.261 g, 72%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 13.6 (s, OH), 7.46–7.38 (m, 5H), 4.01 (q, *J* = 6.8 Hz, 1H), 2.68–2.58 (m, 1H), 1.91–1.66 (m,

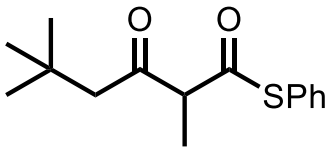
6H), 1.42 (d, J = 6.8 Hz, 3H), 1.34–1.19 (m, 4H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 207.7, 194.8, 134.5, 129.8, 129.4, 127.03, 59.3, 50.3, 29.1, 28.4, 26.1, 25.8, 25.4, 14.0.

General synthesis of β-Keto Thioester from pure acyl chloride



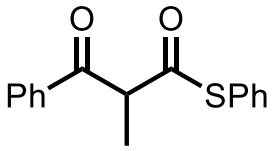
***S*-Phenyl 1-(4-bromophenyl)-3-propane- 1, 3-dione (2.12)**

Solid $MgBr_2 \cdot OEt_2$ (1.38 g, 5.35 mmol) was added to a stirred solution of *S*-phenyl propanethioate (0.27 mL, 1.76 mmol), 4-bromo-benzoyl chloride (0.47 g, 2.16 mmol), and CH_2Cl_2 (6 mL) under Ar atmosphere, and the resulting mixture was stirred for 15 min. Diisopropylethylamine (1.24 mL, 7.13 mmol) was added to the solution, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and reaction mixture was stirred for 12 h. The reaction mixture was then quenched with 10% HCl (4 mL), and the resulting mixture was partitioned between CH_2Cl_2 (15 mL) and water (8 mL). The aqueous phase was washed with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (2 × 15 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a brown solid. Flash chromatography over silica gel using 5:95 EtOAc–hexanes (v/v) gave **2.12** as a white solid (0.597 g, 97%). Spectroscopic data are identical to those given above.



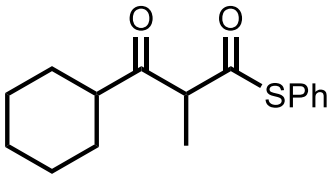
***S*-Phenyl 2-methyl-3-oxo-3-phenylpropanethioate (2.15)**

Procedure was performed as with 2.12 above. Flash chromatography over silica gel using 20:80 CH_2Cl_2–hexanes (v/v) gave **2.15** as a yellow oil (0.404 g, 72%). Spectroscopic data are identical to those given above.



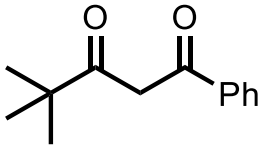
***S*-Phenyl 2,5,5-trimethyl-3-oxohexanethioate (2.13)**

Procedure was performed as with 2.12 above. Flash chromatography over silica gel using 30:70 CH_2Cl_2–hexanes (v/v) gave **24** as a yellow oil (0.405 g, 86%). Spectroscopic data are identical to those given above.



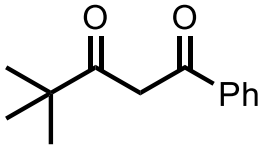
***S*-Phenyl 3-cyclohexyl-2-methyl-3-oxopropanethioate (2.14)**

Procedure was performed as with 2.12 above. Flash chromatography over silica gel using 20:80 CH_2Cl_2–hexanes (v/v) gave **2.14** as a red oil (0.288 g, 59%). Spectroscopic data are identical to those given above.



Large Scale Synthesis of 4,4-Dimethyl-1-phenyl-pentane-1,3-dione (11) Starting from Carboxylic Acid 2.16

Dimethylformamide (0.6 mL, 7.63 mmol) was added to a stirred solution of pivalic acid (6.0 g, 58.7 mmol), oxalyl chloride (15 mL, 174.0 mmol), and CH_2Cl_2 (73 mL) under Ar atmosphere. The solution was stirred for 12 h and then evaporated under reduced pressure to give a mixture consisting of a yellow oil and a dark-brown residue. In a separate flask $MgBr_2 \cdot OEt_2$ (22.5 g, 87.2 mmol) was added to a stirred solution of acetophenone (3.8 mL, 32.6 mmol) and the above-generated yellow oil (5.0 mL; ~40.6 mmol (based on the density of trimethylacetyl chloride)) in CH_2Cl_2 (50 mL) under Ar atmosphere, and the resulting mixture was stirred for 15 min. Di-isopropylethyl amine *i*-Pr_2NEt (21.3 mL, 130.8 mmol) was then added dropwise over ~15 min, the reaction flask was capped with a plastic stopper, sealed with Parafilm, and the mixture was stirred for 12 h. The reaction was quenched with 10% $HCl_{(aq)}$ (35 mL), and the resulting mixture was partitioned between EtOAc (80 mL) and water (40 mL). The aqueous phase was washed with EtOAc (3 × 100 mL) and the combined organic extracts were washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 10:90 EtOAc–hexanes (v/v) gave **2.16** as red oil (5.14 g, 79%). Spectroscopic data are identical to those given above.



Large Scale Synthesis of 4,4-Dimethyl-1-Phenyl-Pentane-1,3-Dione (11) Starting from Acid Chloride 2.17

Solid $MgBr_2 \cdot OEt_2$ (2.3 g, 98.2 mmol) was added to a stirred solution of acetophenone (3.8 mL, 32.6 mmol), trimethylacetyl chloride (5.0 mL, 40.6 mmol), and CH_2Cl_2 (59 mL) under Ar atmosphere, and the resulting reaction mixture was stirred for 30 min. The mixture was cooled in ice-H_2O bath and *i*Pr_2NEt (21.0 mL, 130.0 mmol) was added dropwise over ~15 min. The reaction mixture was allowed to warm to rt and stirred for an additional 4 h. The reaction mixture was then quenched with water (30 mL) and 10% $HCl_{(aq)}$ (35 mL). The resulting mixture was filtered and partitioned between EtOAc (80 mL) and water (40 mL). The aqueous phase was washed with EtOAc (3 × 100 mL) and the combined organic extracts were washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give a red oil. Flash chromatography over silica gel using 10:90 EtOAc–hexanes (v/v) gave **2.17** as a red oil (5.89 g, 89%). Spectroscopic data are identical to those given above.

2.6 Bibliography

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CHAPTER 3

ANTI-α-ALKYLATION OF PHENYL AZOALKENES

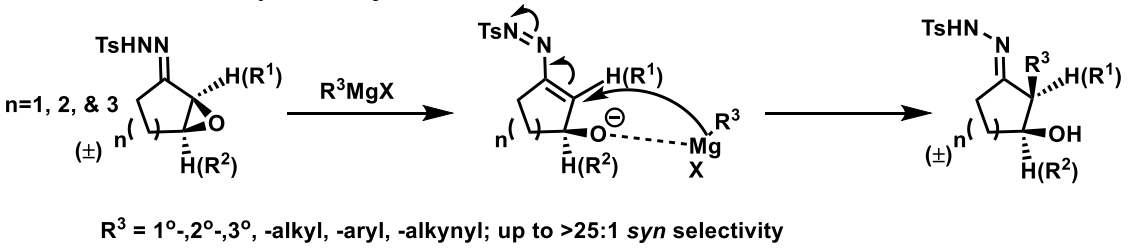
3.1 Introduction

Enolate reactivity is inherently limited by the fact that such carbon-carbon bond formation proceeds in an S_N2 fashion limiting the choice of possible electrophiles.[1] To avoid this problem, an Umpolung-like synthetic strategy can be employed by reacting azo-alkene electrophiles with various organometallic nucleophiles. A tremendous advantage of using this synthetic strategy is that organometallic reagents many contain nucleophilic carbons in all hybridization states, such as sp, sp^2, and sp^3. Varying degrees of steric hindrance in primary, secondary, and tertiary alkyl groups should be compatible with reaction conditions. With these transformations in hand, chemists could achieve easier synthesis of key intermediates for drugs or natural products. The Coltart group has previously reported α-functionalization of α-epoxy *N*-sulfonyl hydrazones, which results in the *syn* α-alkylated products being formed predominately.[2] Although the *anti*-diastereomers were not accessed, other groups have reported their formation using α-epoxy ketones and α-epoxy *N*-oximes using cuprates, Gilman reagents and organolithiums.[3-5] However, limited substrate scope and poor diasterocontrol is characteristic for previous literature methods. In this chapter we will discuss the synthetic methodology development for *anti* α-alkylation of a novel substrates, β-silyated *N*-phenyl azoalkenes. Reactions proceed with good yields and > 25:1 *anti:syn* selectivity using convenient Grignard reagents.

3.2 Results

The 3-alkoxy-1-*N*-sulfonyl azopropenes are intermediates in the Eschenmoser-Tanabe (ET) fragmentation.[6,7] As previously discussed in Chapter 2, the Coltart group has developed an Umpolung-like strategy that involves *syn*-selective α-functionalization of α-epoxy *N*-sulfonyl hydrazones using Grignard reagents (Scheme 3.1).[2] Until recently the *anti*-isomer has not been accessed at high yields and wide substrate scope.

Scheme 3.1 Coltart's Syn α-Alkylation of in situ Formed Azoalkene

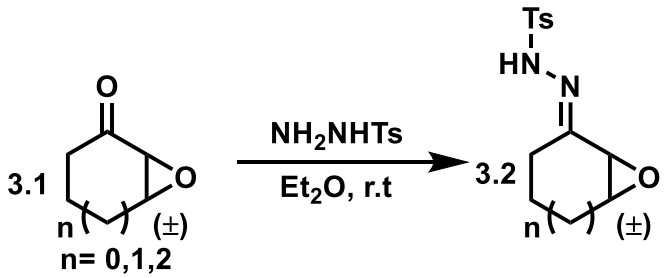


R^3 = 1°-,2°-,3°, -alkyl, -aryl, -alkynyl; up to >25:1 *syn* selectivity

3.2.1 *N*-Sulfonyl α-Epoxide Substrates

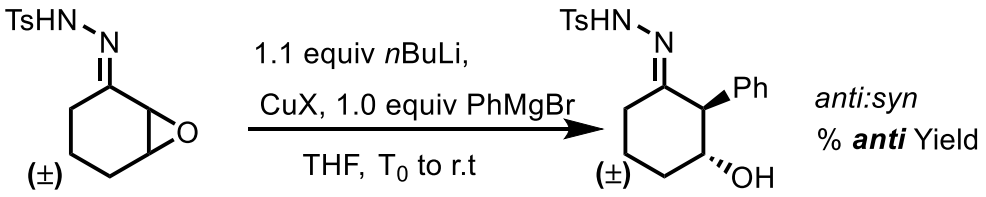
Synthesis of *N*-tosyl α,β-epoxide **3.2** is performed in one step via hydrazone installation onto the epoxy ketone (Scheme 3.2).[2] This substrate has been previously used in the *syn* selective α-alkylation of ketones using Grignard reagents and the stereodivergent control of bicyclic lactones.[2,8] However, researchers have not been successful in using this substrate towards *anti* selective α-alkylation of ketones using Grignard reagents. Initial reaction screens were conducted using cupurates based on works by Corey and Fuchs.[3,4]

Scheme 3.2 Synthesis of N-Tosyl α-Epoxide



A variation of Coltart's syn-selective α-alkylation of *N*-tosyl epoxides using Grignard reagents was used as the control experiment. Instead of using two equivalents of organometallic reagent as in Coltart's original work, one equivalent of *n*BuLi was employed as the base to form the azoalkene in situ while one equivalent of Grignard acted as the alkylating agent (Table 3.1). As expected, the *syn* diastereomer, **entry 3**, was made in >25:1 *syn:anti* selectivity in good yield of 82% with no observable formation of the anti-product. To prevent same face addition, we proposed the use of copper reagents acting as a Lewis acid in hopes of binding to the in situ formed alkoxide to block same face addition of the organometallic reagent. The organomagnesium cuprate that is formed should still act as a 'soft' nucleophile to allow addition at the α-position. To test this hypothesis different copper reagents and temperature variations were explored.

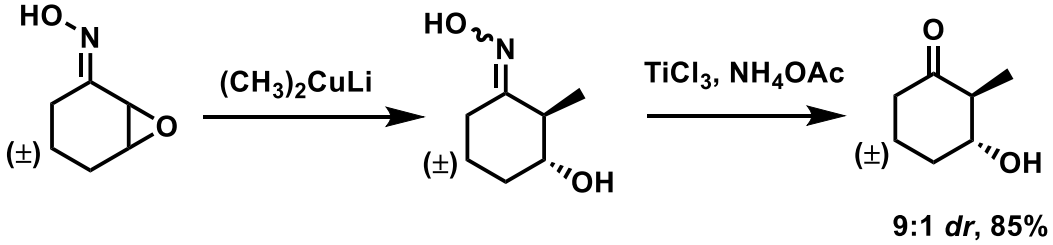
Table 3.1 Reaction Screen Using Magnesium Cuprates



Entry	CuX	Equiv	T_0 (^oC)	*syn* **: *anti***	***anti*** Yield
1	None	0	-78	> 25:1	0% (82% *syn*)
2	CuCN	1.2	-50	N/A	0%
3	CuI	2.4	-50	1:**1**	21% (22% *syn*)
4	CuBr•DMS	2.4	-50	1:**2**	54% (28% *syn*)

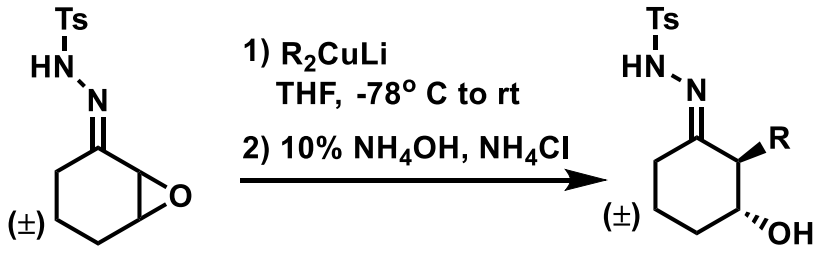
In **entry 2** (Table 3.1) no α-alkylated product was formed using 2.4 equivalents of CuCN. A rationale for lack of formation of either the *syn* or *anti* product could be that CuCN complexed with the Grignard reagent in a fashion that impeded its reactivity. When switching to CuI, a 1:1 mixture of *anti:syn* α-alkylated products were formed. While this reaction conditions gave an improved 21% yield of the desired product, the diastereoselectivity and yield were too low to be synthetically useful. An improved yield was observed when CuBr*DMS was used as a Lewis acid. **Entry 4** shows formation of a 2:1 *anti:syn* mixture with 54% yield of the *anti*-isomer. These conditions doubled the yield in **entry 3**. The rationale for improved yield is likely increased solubility of CuBr*DMS resulting to improved formation of copper reagents.

Scheme 3.3 Corey's Anti α-Alkylation of Oximes



Corey's work with oximes showed fair *anti*-selectivity and good yields when using Gilman reagents (Scheme 3.3).[4] Consequently, we also sought to pursue the use of Gilman reagents for *anti* α-alkylation of *N*-tosyl epoxides. The only variation explored was the type of organolithium and copper halide used to synthesize the Gilman reagent (Table 3.3). The best result is shown in **entry 1**, where two equivalents of phenyl lithium and one equivalent of CuI were used to prepare the Gilman reagent. All reactions were conducted in THF, initial temperature was -78 ^{o}C followed by to warming to room temperature. Reaction was quenched with 10% NH_4OH in sat. $NH_4Cl_{(aq)}$ followed by work up and purification to isolate the desired product. The buffered solution (pH ~6) was used to deactivate the Grignard reagent without causing epimerization at the product α-position. The best result was obtained by employing condition in **entry 1** (Table 3.2), which gave 54% of the *anti*-isomer with a 2:1 *anti:syn* ratio. The conditions in the other entries did give any of the desired α-alkylated product and only a complex mixture was obtained. This suggests that decomposition of the starting material might have occurred.

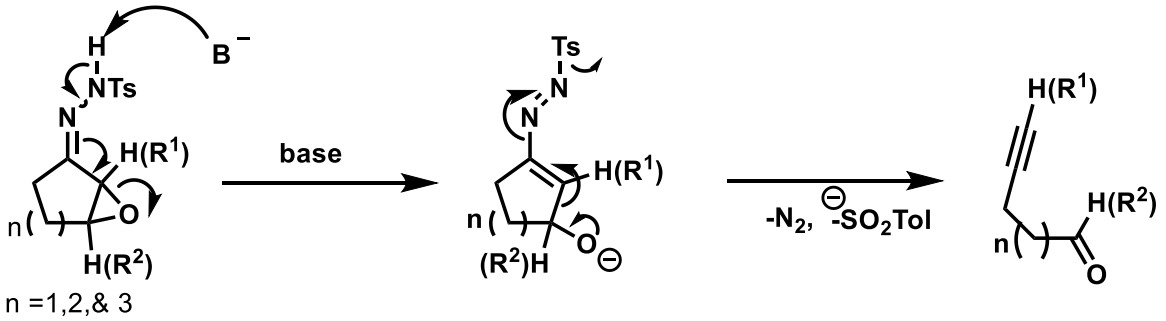
Table 3.2 Reactivity Screen Using Gilman Reagents



Entry	RLi	CuX	%	*dr* (anti:syn)
1	PhLi	CuI	54	2:1
3	*n*-BuLi	CuBr	0	N/A
4	MeLi	CuI	0	N/A

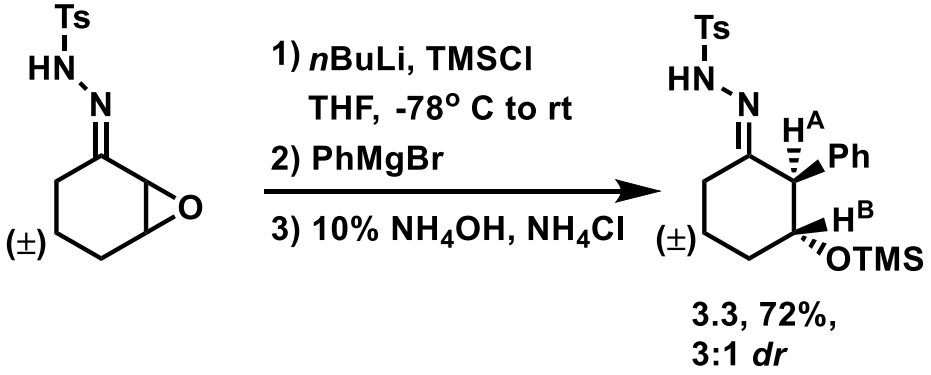
Although yield in **entry 1** (Table 3.2) is the same as observed when using magnesium cuprates, the *anti*-selectivity is still too low to be synthetically useful. We explored many reaction conditions that did not result in formation of α-alkylated product when using either Gilman reagents or organomagnesium cuprates. We can speculate that the problem might lie in the stability of the *in situ* formed azoalkene once *N*-tosyl α-epoxide is opened. It is well known that *N*-tosyl α-epoxides decompose by a rapid Eschenmoser-Tanabe fragmentation forming alkynes (Scheme 3.4). Coltart proposed that reactivity with this very unstable intermediate can be controlled by a dual role of the Grignard reagent.[2] First role of the Grignard reagent is to act as Lewis acid to stabilize the alkoxide to prevent fragmentation. The second role of the Grignard reagent is to act as an alkylating agent. It is possible that using an excess of copper reagent is not a good alternative to control diastereoselectivity as it gives low yield of the desired *anti*-isomer.

Scheme 3.4 Echenmoser-Tanabe Fragmentation



To allow the stabilization of the *in situ* β-hydroxy *N*-tosyl azoalkene, use of *in situ* silylation was explored (Scheme 3.5). To open the epoxide, *n*BuLi was used as the base, followed by slow addition of TMSCl at -78° C. After reacting to form the silylated intermediate, the phenyl Grignard reagent was slowly added, and then the reaction was warmed to room temperature.

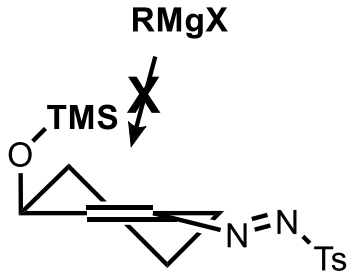
Scheme 3.5 Anti-α- Alkylation Using in situ Silyl Protection



Subsequent quenching with a buffered solution of 10 mol % NH_4OH and NH_4Cl (pH ~ 6) gave, the desired *anti* α-alkylated product in 72% yield and 3:1 *anti:syn* isomer ratio. Rationale for the higher *anti* diastereoselectivity is as follows. The bulky trimethylsilyl ether is effective in blocking same face nucleophilic addition by the Grignard reagent (Figure 3.1). Characterization of the *anti*-diastereomer was performed by measuring the *J* coupling constant between H^A and H^B in compound 3.3 (Scheme 3.5). With respect to the ^{1}H-NMR obtained,

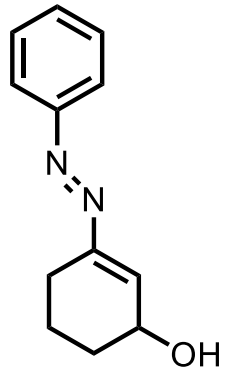
regardless of the environment associated in the rest of the molecule as long as the H^A multiplicity is only affected by H^B, one can get an accurate determination of the orientation (i.e. *anti*- or *syn*-) of H^A in respect to H^B. The *J* coupling of H^A (Scheme 3.1) of the *syn* alkylated species is reported to between 4 and 6 Hz based on similar structures in literature. For the *anti* α-proton H^A-H^B *J*-coupling constant is expected to be 8 Hz or larger based on similar structures found in literature.[3,5]

Figure 3.1 Proposed Model for in situ Silylation of β-Hydroxy N-Tosyl Azoalkene



The methodology proved difficult to reproduce. Because of this issue, another substrate was considered to form a more stable β-hydroxy azoalkene. It was suspected poor reproducibility of the results were observed due to the instability of the β-hydroxy *N*-tosyl azoalkene (Scheme 3.4). To prevent decomposition of the starting material, a more thermally stable azoalkene was selected (Figure 3.2). The phenyl β-hydroxy azoalkene **3.4** was initially prepared by Dr. Thien Nguyen. Compound **3.4** (Figure 3.2) is both thermally and air stable, however, until recently it had not been modified to be used towards substrate controlled *anti*-α-alkylation using Grignard reagents, which will be discussed later in this chapter.

Figure 3.2 *E* (1-Cyclohexenyl-3-ol)phenyldiazine



3.4

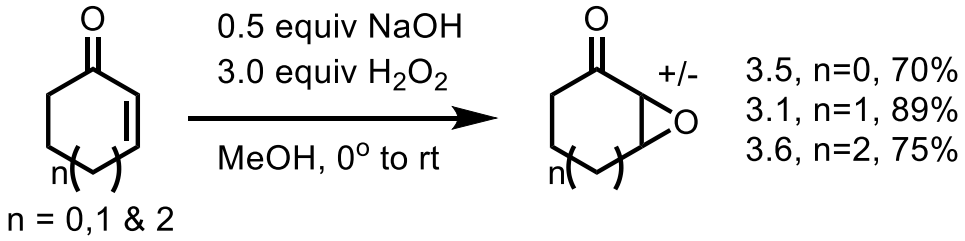
The air and thermally stable β-silylated phenyl azoalkene is formed in its *E* configuration. Aryl azoalkenes can exist as *E* or *Z* isomers .[9] The *E*-phenyl azoalkene is usually the thermodynamic product. An equilibrium can be established between the two isomers, but this is strongly dependent on the substitution on the aryl group. Isomerization can be observed upon UV irradiation or upon heating.[10] To note such studies only been conducted on azoalkenes not possessing any functional groups at the β-position. Our data shows that only the *E* azoalkene is formed and does not equilibrate to form the *Z*-isomer. Compound 3.4 could be left under incandescent light for several days without any change in the ^{1}H-NMR and ^{13}C-NMR spectra.

3.2.2 Synthesis of β-Silylated Azoalkenes

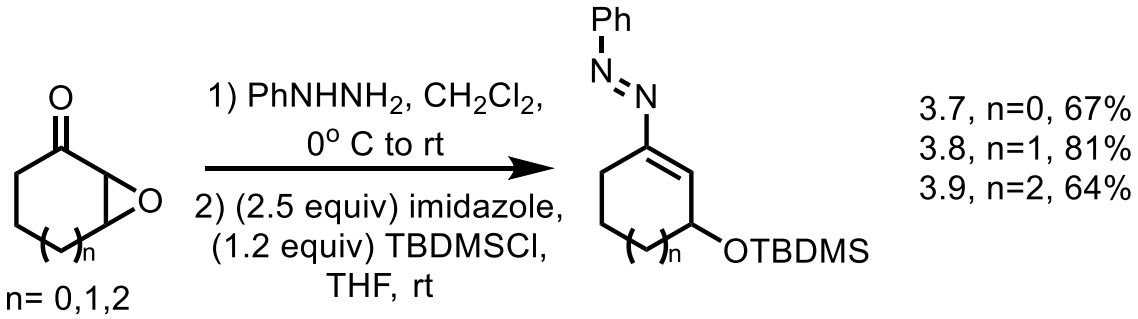
The synthesis of β-silylated phenyl azoalkenes can be carried out in three steps. This novel substrate is prepared from commercially available cyclohexen-2-one. First, the alkene is converted to the epoxide by a base catalyzed reaction using hydrogen peroxide oxidant (Scheme 3.6). This methodology works on 5- and 7- membered rings as well, providing 70% to 89% yields, respectively. With the epoxide in hand, it was then subjected to hydrazone installation by using phenylhydrazine to form the desired β-hydroxy phenyl azoalkenes in good yields. The

azoalkene can then be silylated using *tert*-butyl dimethyl silyl chloride to afford the air and thermally stable β-silated phenyl azoalkenes (Scheme 3.7). This methodology also works on five and seven membered ring substrates.

Scheme 3.6 Synthesis of α,β-Epoxy Ketones



Scheme 3.7 Synthesis of β-Silylated Phenyl Azoalkenes

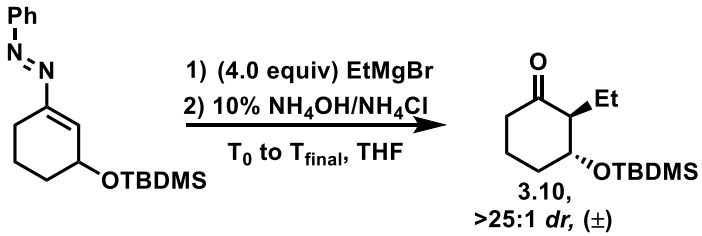


3.2.3 *Anti*-α Alkylation of β-Silylated Phenylazoalkenes

A reaction screen was used to test the reactivity of β-silyated phenyl azoalkenes in formation of the *anti* α-alkylated products. To our delight, direct α-alkylation of the azoalkene was observed (Table 3.3). The silylated azoalkene was alkylated using an excess of ethyl magnesium bromide, and variation in initial and final reaction temperature was explored. The reaction was quenched with 10 mol% NH_4OH in NH_4Cl (pH ~ 6) to deactivate the Grignard reagent without causing α-epimerization of the product. The alkylated hydrazone that was

formed was worked up with acetone to extract organic compound and to help facilitate hydrazone removal.

Table 3.3 Reaction Screen using β-Silylated Phenyl Azoalkene



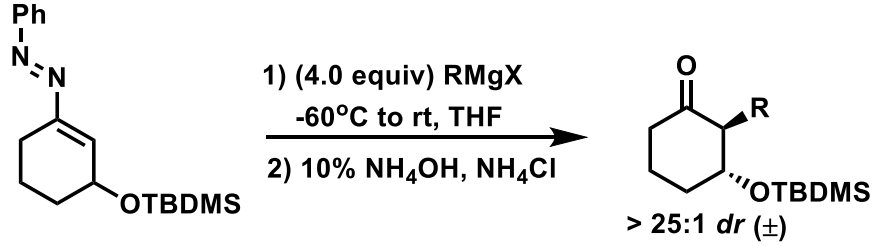
Entry	T_0 (°C)	T_{final} (°C)	%Yield
1	0	0	0%
2	-70	-70	0%
3	-60	25	79%
4	-85	25	84%

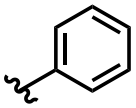
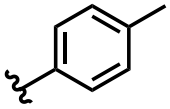
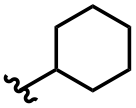
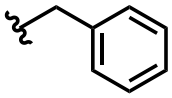
For **entries 1** and **2** (Table 3.3) temperatures were maintained at 0 ° or -70 °C for the entire course of the reaction and no reaction occurred. However, as shown in **entry 3**, if the reaction temperature is increased from -60 °C to r.t., 79% of desired *anti*-product was isolated with a remarkably high diastereoslectivity of >25:1 *anti:syn*. The diastereomeric ratio is based on ^{1}H-NMR analysis of the crude reaction mixture. The spectra were also compared against the spectra of *syn* diastereomer of the β-hydroxy α-alkylated ketones and known *anti* β-hydroxy α-alkylated ketone synthesized under different reaction conditions.[3,5] The *J*-coupling constant H^A-H^B in compound **3.10** (Table 3.3) is difficult to determine due to coupling with the adjacent ethyl group. To help elucidate the spatial orientation of H^A-H^B of compound 3.6 in orientation to each other, selective 1-D NOE experiment was used. The NMR experiment was conducted by selectively irradiating H^B, signal at 4.31 ppm. For selective 1-D NOE experiments a peak of

interest, in this case at 4.13 ppm, can be manually selected and its neighbors/atoms which are in proximity show an NOE enhancement. If the neighboring atom/group is not in proximity no enhancement or additional peak is observed. This only works for neighboring atoms that are three bonds away or less from the atom of interest. If the H^B is *syn* to H^A then an additional signal/enhancement of the H^A peak will be observed but if the H^B is *anti* to H^A then no additional signal/no enhancement will be observed.[11] As expected, after performing the selective 1-D NOE there was no observable peak of H^A which would be expected to occur between 3.0 ppm and 2.0 ppm hence confirming that H^A is anti with respect to H^B.

The highest yield was obtained by performing reaction at -85 ^oC as the initial temperature. and warming the reaction solution to room temperature. However, due to technical issues the use of -60 ^oC temperature was more practical. With improved reaction conditions in hand, a substrate screen was performed to test the compatibility of this methodology with different functionality at the α-position (Table 3.4).

Table 3.4 Substrate Scope for *Anti* α-Alkylation



Entry	R	% Yield	Entry	R	% Yield
1		83%	6		53%
2		88%	7		80%
3		83%	8		52%
4		42%	9		96%
5		76%			

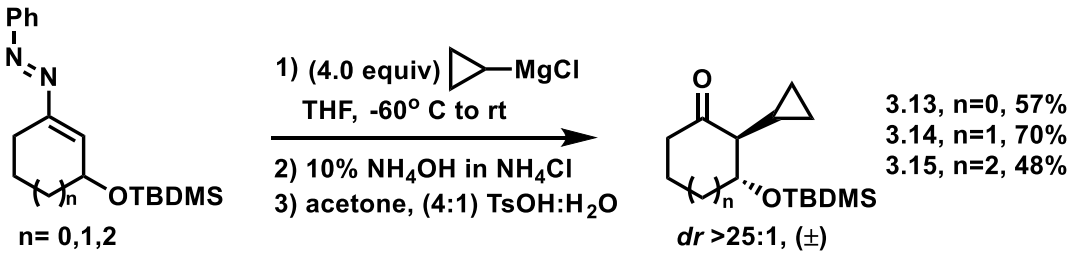
The use of primary, secondary and tertiary alkyl Grignard reagents shown in **entries 1** to **3** gave the desired anti α-alkylated ketones in excellent yields ranging from 83% to 88%. Vinyl Grignard (**entry 4**) is also compatible with reaction condition, but a lower yield of 42% was obtained. Benzylic Grignard gave product in 76% yield (**entry 5**). Both phenyl (**entry 6**) and tolyl (**entry 7**) Grignard reagents gave the desired *anti*-products in 53% and 80% yields, respectively. The use of cyclic alkyl Grignard reagents such as cyclohexyl- (**entry 8**) and cyclopropyl- (**entry 9**) also worked well giving product yields of 52% and 96%, respectively. All products shown in Table 3.5 were formed with excellent *anti* diastereoselectivity of >25:1

anti:syn. This ratio is based on the ^{1}H-NMR analysis of the crude reaction mixtures. Characterization of the compounds were performed in the same manner as discussed previously.

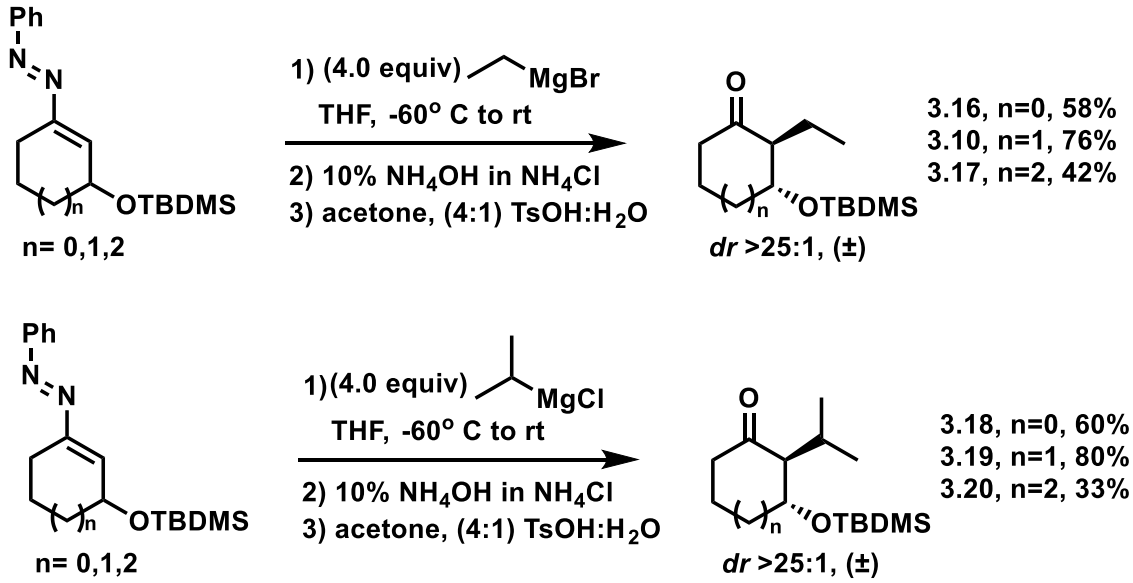
3.2.4 *Anti*-α Alkylation of 5 and 7 Membered Ring β-Silylated Phenyl Azoalkenes

The same reaction conditions were applied to 5- and 7- membered ring azoalkenes. Hydrazone removal after quenching the reaction with the buffered solution was performed under harsher conditions than those used for the 6 membered ring. The six- membered ring azoalkenes where also subjected to the same hydrazone removal conditions to allow for an accurate comparison of yields between substrates with different ring sizes. Cyclopropyl-, isopropyl-, and ethyl- Grignard reagents were used to test the reactivity of 5- and 7- membered rings. All substrates reacted with the Grignard reagents providing fair to good yields of the α-alkylated products while maintaining the high diasteroselectivity of >25:1 *anti:syn* dr (Schemes 3.8 and 3.9).

Scheme 3.8 Anti α-Alkylation of 5-,6- and 7-Membered Azoalkenes with Cyclopropyl Grignard Reagent



Scheme 3.9 Anti α-Alkylation of 5-,6- and 7-Membered Azoalkenes with Grignard Reagents

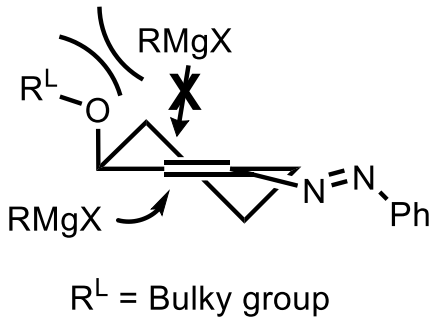


The 5-membered ring substrates reacted with cyclopropyl magnesium chloride followed by hydrazone removal during workup to give the desired *anti* product in 57% yield. The 7-membered ring substrate notably gave a lower yield of 48% in the same reaction. Reaction of ethyl magnesium bromide with the 5-membered and 7-membered ring substrates produced the desired *anti* isomers in 58% and 42% yields, respectively. Lastly, *iso*-propyl magnesium chloride was reacted with the 5- and 7-membered ring substrates yielding the desired products in 60% and 33% yields, respectively. The overall lower yields for the 5- and 7- membered ring substrates are due to decomposition of the starting material during the hydrazone removal step. The 6-membered ring substrate gives lower product yield if using 4:1 solution of TsOH:H_2O workup procedure hence supporting the hypothesis.

3.3 Discussion

The rationale for obtaining high *anti*-alkylation diastereoselectivity for the 5-, 6-, and 7-membered ring substrates is proposed in the model shown below (Figure 3.3). We propose that the bulky TBDMS group blocks same face addition of the Grignard reagent at the α-position by steric hindrance. We believe that the β-silyl group is in the pseudo axial position. The pseudo axial position explanation is preferred as it gives a better explanation of the high *anti* diastereoselectivity obtained.

Figure 3.3 Proposed Model Explaining High Anti-Diasteroselectivity



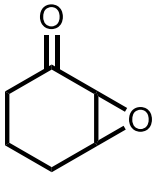
The α-functionalization of ketones using an Umpolung-like approach provides advantages compared to the conventional enolate strategy. As discussed in Chapter 1, substrate scope limitation for conventional enolate reactivity is due to inherent limitations of S_N2-like reactions. β-Silylated phenyl azoalkene precursor allows nucleophilic addition by *t*-butyl, and sp^2 hybridized groups such as phenyl and vinyl to occur well. Using such functionality in high yields using a conventional enolate strategy would be nearly impossible. However, sp-hybridized alkynyl magnesium reagents are not compatible with our reaction conditions.

3.4 Conclusions

The research described in Chapter 3 lead to the development of the novel *anti*-selective α-alkylation of β-silylated phenyl azoalkenes. This synthetic methodology also allowed for expansion of the substrate scope to include 5- membered and 7- membered ring substrates. The reaction allows for indirect stereocontrol in α-alkylated-ketones which will contribute to expanding useful and selective methods for the synthesis of natural products and small molecules. Given the general importance of carbonyl α-functionalization in organic chemistry, our method could be widely used in the synthesis of important and structurally challenging compounds.

3.5 Experimental Section

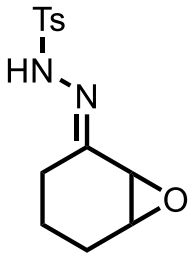
All reactions were carried out in dried solvents under a slight static pressure of prepurified quality Ar that had been passed through a 5 x 20 cm column of Drierite. Glassware was dried in an oven at 120 ^{o}C for at least 12 h prior to use and then either cooled in a desiccator cabinet over Drierite or assembled quickly while hot, sealed with rubber septa, and allowed to cool under a stream of Ar. Dry solvents were obtained using an Innovative Technologies solvent purification system. Commercial grade solvents were used for routine purposes without further purification. Amines were distilled from CaH_2 under N_2 atmosphere prior to use. Column chromatography was performed on 230-400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometers at ambient temperature. High-resolution Mass Spectrometry was acquired using an Agilent Technologies 6530 Accurate Mass Q-Tof LC-MS for electrospray ionization (ESI) or a Micromass Autospec Ultima for chemical ionization (CI).



7-Oxabicyclo[4.1.0]heptan-2-one (3.1)

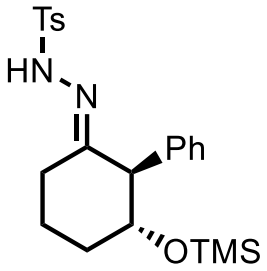
Cyclohexanone (13 mL, 134.3 mmol) of was added to MeOH (300 mL) in a 500 mL round bottom flask equipped with a stir bar, and a rubber septum. The colorless solution was subsequently cooled to 0 ^{o}C using an ice bath and aqueous NaOH (40 mL of 20% w/v) was then added dropwise and temperature maintained at 0 ^{o}C. The reaction solution was warmed to room temperature and stirred for 2 h. The reaction was quenched with water (30 mL) followed

by extraction with dichloromethane (4 x 80 mL). The combined organic layer was then dried over $MgSO_4$ filtered, and solvent removed under reduced pressure using a rotovap. To further remove any water, the product was placed into a vial which was placed in a chamber half filled with drierite under high vacuum for 30 min. Compound 3.1 was obtained as a colorless oil (13.1 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 2.51 (t, *J* = 4.4 Hz, 1H), 2.28-2.24 (m, 1H), 2.11-2.03 (m, 1H), 1.99-1.87 (m, 2H), 1.72-1.61 (m, 2H);^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, ppm): δ 205.7, 55.7, 55.1, 36.1, 22.6, 16.5. This compound is known.[12]



N'-(7-Oxabicyclo[4.1.0]heptan-2-ylidene)-4-methylbenzenesulfonohydrazide (3.2)

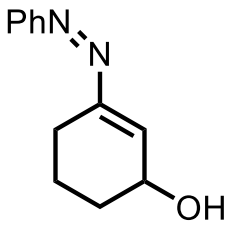
To a 25 mL round bottom flask and stir bar was added **3.1 (**1.5 g, 0.013 mmol) and Et_2O (15 mL). Subsequently, p-toluene sulfonyl hydrazine (0.81 g, 4.35 mmol) was added to the solution. The reaction was stirred for 3 h at room temperature under Ar. A cloudy white precipitate formed and then the solution was filtered. The solid collected was washed with Et_2O (3 x 25 mL). The resultant white solid can be recrystallized from EtOAc or used as is. Product was obtained as a white solid (1.09 g, 87%).^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.86 (d, *J*=8.2 Hz, 2H), 7.50 (s, 1H), 7.31 (d, *J*=8.0 Hz, 2H), 3.53-3.51 (m, 1H), 3.48-3.46 (m, 1H), 2.44 (s, 3H), 2.28-2.14 (m, 2H), 1.83-1.66 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, ppm): δ 152.4, 144.5, 129.8, 128.1, 54.1, 53.3, 23.8, 23.1, 21.7, 14.4.This compound is known.[2]



***(trans*)-2-Phenyl-3-((trimethylsilyl)oxy)cyclohexylidene) benzenesulfonohydrazide (3.3)**

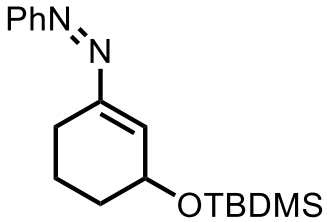
Compound **3.2** (0.18 mmol, 50.0 mg) was dissolved in THF (3 mL) inside a flame dried 10 mL round bottom flask equipped with a stir bar. The solution was cooled to -78^{o} C using an immersion cooler. In a separate flame-dried round bottom flask was placed phenyl magnesium bromide (0.36 mmol, 0.4 mL in ether) diluted with THF (2.0 ml). Grignard reagent is titrated with 2-hydroxybenzaldehyde phenyl hydrazone before use. Added n-BuLi (0.19 mmol, 80 uL in THF) dropwise to epoxide solution. Stirred for 2 min then TMSCl (0.18 mmol, 23 uL) added. Reaction allowed to stir at -78^{o} C for 12 min. Diluted Grignard solution was added to the *in situ* azoalkene via syringe over ~ 15 min. After addition of the reaction was stirred at -78 ^{o}C for 2 hours 30 min. The mixture was then quenched with 10% NH_4OH in sat. $NH_4Cl_{(aq)}$ (5 mL) and stirred for 15 min followed by addition of water (5 mL). Extraction with EtOAc (3 x 20 mL) then washed combined organic with brine (10 mL) followed by drying over $MgSO_4$ filtration, and solvent removed under reduced pressure gave a crude product. Purification by column chromatography with 50% EtOAc in hexanes. White solid (60.0 mg, 72 %) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.75 (d, *J*=8.4 Hz, 2H), 7.37 (d, *J*=8.4 Hz, 2H), 7.13-7.04 (m, 5H), 3.91 (dt, *J*=4.4 Hz, *J*=4.0 Hz, 2H), 3.30 (d, *J*= 8.8 Hz, 1H), 2.59-2.52 (m, 2H), 2.39 (s, 3H), 2.02-1.97 (m, 1H), 1.95-1.84 (m, 2H), 1.66-1.56 (m, 1H), -0.21 (s,

9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 160.9, 143.8, 138.4, 134.6, 129.1, 128.3, 127.8, 74.6, 59.5, 34.3, 25.9, 21.7, 20.9, -0.081.



***E* (1-Cyclohexenyl-3-ol) phenyldiazine (3.4)**

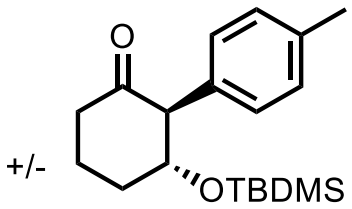
In a 25 mL round bottom flask **3.1** (1.82 g, 9.01 mol) was dissolved in CH_2Cl_2 (10 mL) followed by addition of phenyl hydrazine (1.95 g, 18.0 mol). The mixture was stirred overnight at room temperature. Solvent was removed under reduced pressure and the red crude solid was purified using silica column chromatography using 5% EtOAc in hexanes eluent. Red solid (1.71 g, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.77-7.75 (m, 2H), 7.49-7.40 (m, 3H), 6.90-6.88 (m, 1H), 2.43-2.39 (m, 2H), 2.09-2.03 (m, 1H), 1.99-1.91 (m, 1H), 1.77-1.67 (m, 3H), 1.56 (2, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 152.4, 140.6, 130.7, 129.1, 122.6, 66.9, 60.5, 32.2, 22.6, 18.9.



(E)-1-(3-((tert-butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)-2-phenyldiazene (3.8)

Compound **3.4** (6.92 mmol, 1.4 g) was dissolved in CH_2Cl_2 (10 mL) in a 25 mL round bottom flask equipped with a stir bar. Imidazole (17.3 mmol, 1.2 g) was added, followed by TBDMSCl

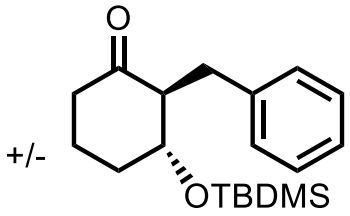
(8.31 mmol, 1.3 g). The reaction was stirred at room temperature under Ar for 4 hr. Subsequently it was diluted with water (10 mL) and stirred for 10 min. Reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with sat. $NaCl_{(aq)}$ (50 mL) and dried over $MgSO_4$, filtered and solvent was removed under reduced pressure. The residue was purified using silica column choromatography using 20% EtOAc in hexanes eluent. Red-orange solid (1.77 g, 81%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ ; 7.77-7.73 (m, 2H), 7.49-7.38 (m, 3H), 6.79-6.83 (m, 1H),4.63-4.71 (m, 1H), 3.74 (t, *J* = 4.0 Hz, 1H), 2.46-2.34 (m, 2H), 2.11-2.03 (m, 1H), 1.99- 1.91 (m, 2H), 1.89-1.84 (m, 1H), 0.931 (s, 9H), 0.138 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, ppm): δ 155.3, 152.9, 142.8, 130.3, 129.1, 122.5, 67.8, 32.6 26.0, 22.6, 19.3, 18.2, -4.2.



(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-(p-tolyl)cyclohexanone (3.21)

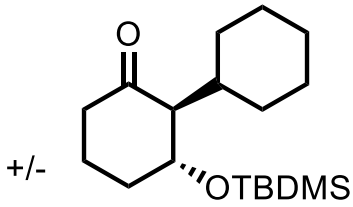
Compound **3.8** (0.130 mmol, 41.1 mg) was dissolved in THF (0.4 mL) inside a flame dried 10 mL round bottom flask equipped with a stir bar. The solution was cooled to -65 ^{o}C using an immersion cooler. In a separate flame-dried round bottom flask was placed tolyl magnesium bromide (0.52 mmol, 0.56 mL in ether) diluted with THF (0.4 ml). Grignard reagent is titrated with 2-hydroxybenzaldehyde phenyl hydrazone before use. Diluted Grignard solution was added to the azoalkene solution via syringe over ~ 15 min. After addition of the Grignard reaction was stirred at -60 ^{o} C for 15 min then slowly warmed to room temperature. The mixture

was stirred at rt overnight followed by quenching with 10% NH_4OH in sat. $NH_4Cl_{(aq)}$ (5 mL) and stirring for 40 min. Extraction with acetone (3 x40 mL) followed by drying over $MgSO_4$, filtration, and solvent removed under reduced pressure gave a crude product. Purification by column chromatography with 5% EtOAc in hexanes. Brown oil (32.8 mg, 80 %) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.12 (d, *J*= 8.0, H, 2H), 6.98 (d, *J*=7.6 Hz, 2H), 3.98 (dt, *J*=4 Hz, 1H), 3.51 (d, *J*= 9.2 Hz, 1H), 2.51-2.45 (m, 1H), 2.42-2.38 (m, 1H), 2.19-2.14 (m, 1H), 2.10-2.02 (m, 1H), 1.87-1.77 (m, 1H), 1.69-1.61 (m, 1H), 0.692 (s, 9H), -0.218 (s, 3H), -0.476 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 208.8, 136.5, 133.5, 129.7, 128.9, 75.9, 66.6, 41.0, 34.5, 25.7, 21.2, 20.6, 17.9, -4.75, -4.69.



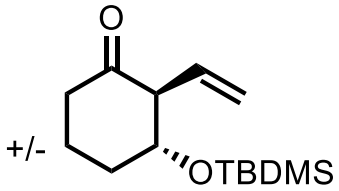
(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-benzyl-cyclohexanone (3.22)

The procedure was performed same as for **3.21**, using **3.8** (0.164 mmol, 51.7 mg) and benzyl magnesium bromide (0.66 mmol, 0.6 mL in ether). Brown oil (39.0 mg, 76%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 7.52-7.61 (m, 5H), 3.67 (td, *J*=3.2 Hz, 1H), 2.97-2.83 (m, 2H), 2.70-2.65 (m, 1H), 2.39-2.33 (m, 1H), 2.29-2.22 (m, 1H), 2.10-1.97 (m, 2H), 1.75-1.68 (m, 2H), 1.75-1.68 (m, 1H), 1.54 (s, 2H), 0.885 (s, 9H), 0.015 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 210.7, 140.715, 129.2, 128.4, 126.0, 74.1, 62.1, 40.7, 32.8, 32.7, 25.9, 21.0, 18.1, -4,81,-4.3.



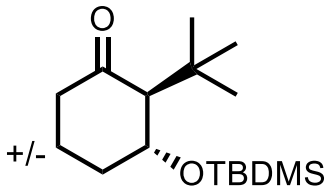
(*trans*)-6-((tert-butyldimethylsilyl)oxy)-[1,1'-bi(cyclohexan)]-2-one (3.23)

The procedure was performed same as for **3.21**, using **3.8** (0.149 mmol, 47.3 mg) and cyclohexyl magnesium chloride (0.60 mmol, 0.4 mL in ether). Oil (24.0 mg, 52%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 4.31 (m, 1H), 2.33-2.19 (m, 2H), 2.13-2.03 (m, 2H), 1.92-1.84 (m, 3H), 1.79-1.50 (m, 7H), 1.40-1.35 (m, 1H), 1.27-1.12 (m, 2H), 1.05- 0.941 (m, 2H), 0.838 (s, 9H), 0.006 (s, 6H) ; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 213.8, 71.3, 65.6, 39. 5, 37. 6, 31. 6, 30. 9, 28.3, 26.3, 26.3, 26.2, 25.8, 20.9, 18.1, -4.771, -4.819.



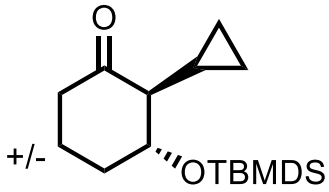
(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-vinylcyclohexanone (3.24)

The procedure was performed same as for **3.21**, using **3.8** (0.196 mmol, 62.2 mg) and vinyl magnesium chloride (0.78 mmol, 0.9 mL in ether). Oil (28.0 mg, 42%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 6.29-6.12 (m, 2H), 6.10-6.09 (m, 1H), 5.14 (dt, J = 4.2 Hz, 1H), 4.94-4.90 (m, 1H), 2.53-2.50 (m, 1H), 2.44-2.41 (m, 1H), 2.31-2.26 (m, 1H), 2.23-2.18 (m, 2H), 1.99-1.92 (m, 3H), 1.90-1.86 (m, 3H), 0.82 (s, 9H), 0.06 (s, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 208.1, 129.2, 113.2, 72.3, 48.3, 32.4, 31.7, 29.4, 25.8, 20.0, -4.6, -4.8 .



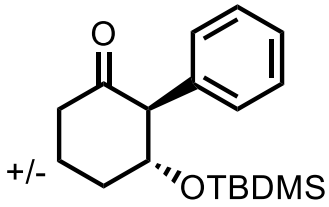
(*trans*)-2-(tert-butyl)-3-((tert-butyldimethylsilyl)oxy)cyclohexanone (3.25)

The procedure was performed same as for **3.21**, using **3.8** (0.293 mmol, 92.8 mg) and *t*-butyl magnesium bromide (1.17 mmol, 2.3 mL in ether). Oil (69.0 mg, 83%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 4.21-4.30 (m, 1H), 2.67-2.73 (m, 1H), 1.92-1.81 (m, 3H), 1.62-1.54 (m, 2H), 1.30-1.22 (m, 1H), 0.933 (s, 9H), 0.841 (s, 9H), 0.064 (s, 3H), 0.032 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 210.3, 74.6, 61.6, 41.5,33.2, 31.1, 27.9, 25.8, 18.9, 18.0, -4.972, -4.853.



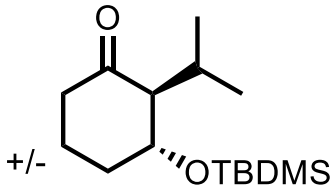
(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-cyclopropylcyclohexanone (3.14)

The procedure was performed same as for **3.21**, using **3.8** (0.27 mmol, 85.5 mg) and cyclopropyl magnesium chloride (1.1 mmol, 1.1 mL in ether). Oil (70.0 mg, 96%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 4.13 (m, 1H), 2.53-2.44 (m, 1H), 2.30-2.24 (m, 1H), 2.17-1.98 (m, 2H), 1.78-1.69 (m, 3H), 1.50 (dd, *J*=4.0 Hz, 1H), 1.0-0.89 (m, 1H), 0.85 (s, 9H), 0.80-0.65 (m, 1H), 0.60-0.46 (m, 2H), 0.22 (d, *J*=4.4 Hz, 1H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 212.7, 74.6, 64.6, 39. 4, 30.1, 25.8, 20. 7, 18.1, 11.1, 4.9, 3.3, -4.7, -4.9.



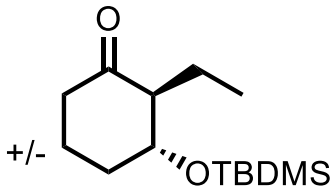
(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-(phenyl)cyclohexanone (3.26)

The procedure was performed same as for **3.21**, using **3.8** (0.147 mmol, 46.5 mg) and phenyl magnesium bromide (0.59 mmol, 0.80 mL in ether). Oil (23.7 mg, 53%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 7.36-7.31 (m, 1H), 4.02 (dt, *J*=4.4. Hz, 1H), 3.58 (d, *J*=10.0 Hz, 1H), 2.61-2.31 (m, 5H), 2.14-2.09 (m, 2H), 0.91 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 208.2, 136.7, 130.0, 128.2, 127.1, 76.1, 67.0, 41.1, 34.9, 25.6, 20.6, 17.9, -4.7.



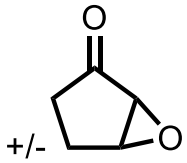
(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-isopropylcyclohexanone (3.19)

The procedure was performed same as for **3.21**, using **3.8** (0.147 mmol, 4.65 mg) and *iso*-propyl magnesium bromide (0.59 mmol, 0.76 mL in ether). Oil (41.0 mg, 88%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 4.22-4.21 (m, 1H), 2.49-2.46 (m, 1H), 2.38-2.25 (m, 2H), 2.05-1.93 (m, 1H), 1.89-1.81 (m, 2H), 1.70-1.60 (m, 3H), 1.55 (d, *J*=8.9Hz, 6H), 0.80 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 212.1, 70.3, 64.9, 51.8, 57.5, 27.2, 26.7, 26.2 23.9, 16.3, -0.664 .



(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-ethylcyclohexanone (3.10)

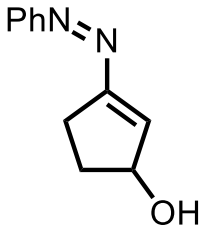
The procedure was performed same as for **3.21**, using **3.8** (0.437 mmol, 13.8 mg) and ethyl magnesium bromide (1.75 mmol, 1.86 mL in ether). Oil (35.0 g, 83%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 4.30-4.26 (m, 1H), 3.81-3.77 (m, 1H), 2.37-2.18 (m, 3H), 2.10-1.95 (m, 2H), 1.90-1.77 (m, 2H), 1.70-1.56 (m, 5H), 0.87 (s, 9H), 0.84 (t, *J*=4.7 Hz, 3H), 0.04 (s, 6H), 0.025-0.019 (m, 2H) ; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, ppm): δ 212.3, 74.1, 61.3, 40.0, 31.8, 25.8, 20.8, 20.7, 18.1, 12.2, -4.4.



2,3-epoxycyclopentanone (3.5)

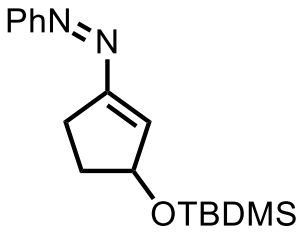
Cyclopentenone (41.3 mmol, 3.5 mL) was added to MeOH (50 mL) in a 100 mL round bottom flask equipped with a stir bar, and rubber septum. The colorless solution was subsequently cooled to 0 ^{o}C using an ice bath and aqueous NaOH (12 mL of 20% w/v) was then added dropwise and temperature maintained at 0 ^{o}C. The reaction solution was warmed to room temperature and stirred for 2 h. The reaction was quenched with water (15 mL) followed by extraction with dichloromethane (4 x 50 mL). The combined organic was then dried over $MgSO_4$ filtered, and solvent removed under reduced pressure using a rotovap. To further remove any water, the product was placed into a vial which was placed in a chamber half filled

with drierite under high vacuum for 30 minutes. Obtained colorless oil (3.86 g, 95%).^{1}H NMR ($CDCl_3$, 400 MHz, ppm): δ 5.19- 5.0 (m, 1H), 3.74-3.68 (m, 1H), 3.09-2.73 (m, 1H), 2.19-1.97 (m, 2H), 1.93-1.74 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 211.1, 61.0, 53.6, 31.3, 22.3.



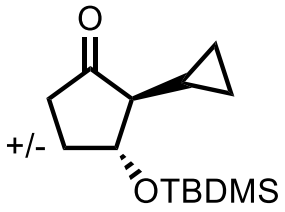
(E) (1-Cyclopentenyl-3-ol) - phenyldiazine (3.11)

In a 25 mL round bottom flask **3.5** (31.89 mmol, 3.1 g) was dissolved in CH_2Cl_2 (15 mL) followed by addition of phenyl hydrazine (28.7 mmol, 2.8 mL). The mixture was stirred overnight at room temperature. Solvent was removed under reduced pressure and the red crude solid was purified using silica column chromatography using 5% EtOAc in hexane eluent. Red oil (4.50, 75%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 7.77-7.75 (m, 2H), 7.49-7.40 (m, 3H), 6.90-6.85 (m, 1H), 2.43-2.39 (m, 2H), 2.09-2.03 (m, 1H), 1.99-1.91 (m, 1H), 1.77-1.67 (m, 3H), 1.56 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 151.5,137.0, 129.1, 124.7, 122.0, 119.1, 72.6, 32.8, 29.3.



(*E*)-1-(3-((tert-butyldimethylsilyl)oxy)cyclopent-1-en-1-yl)-2-phenyldiazene (3.7)

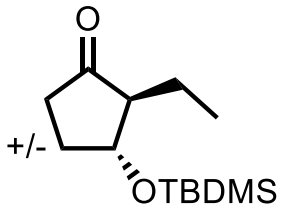
Compound **3.5** (3.48 mmol, 0.66 g) was dissolved in CH_2Cl_2 (5 mL) in a 25 mL round bottom flask equipped with a stir bar. Imidazole (8.7 mmol, 0.59 g) was added, followed by TBDMSCl (4.2 mmol, 0.63 g). The reaction was stirred at room temperature under Ar for 4 h. Subsequently it was diluted with water (10 mL), and stirred let mix for 10 min. Reaction mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layer was then washed with sat. $NaCl_{(aq)}$ (20 mL) and dried over $MgSO_4$ filtered, and solvent was removed under reduced pressure. The residue was purified using silica column chromatography using 20% EtOAc in hexanes eluent. Yellow oil (0.74 g, 70%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 7.78-7.76 (m, 1H), 7.58-7.39 (m, 4H), 6.80-7.78 (m, 1H), 5.16-5.12 (m, 1H), 2.91-2.78 (m, 2H), 2.58-2.37 (m, 3H), 1.99-1.84 (m, 1H), 0.93 (s, 9H), 0.14 (s, 6H) ; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 151.3, 140.0, 129.1, 127.3, 120.9, 74.4, 31.5, 24.7, 24.2, 16.6, -0.69.



(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-cyclopropylcyclopentanone (3.13)

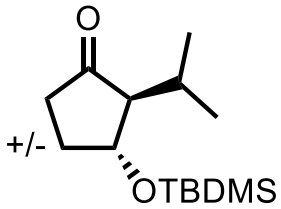
Compound **3.7** (0.229 mmol, 69.5 mg) was dissolved in THF (0.4 mL) inside a flame dried 10 mL round bottom flask equipped with a stir bar. The solution was cooled to -65 ^{o}C using an

immersion cooler. In a separate flame-dried round bottom flask cyclopropyl magnesium chloride (0.919 mmol, 0.92 mL in ether) was diluted with THF (0.8 ml). Grignard reagent was titrated with 2-hydroxybenzaldehyde phenyl hydrazone before use. Diluted Grignard solution was added to the azoalkene solution via syringe over ~ 15 min. After addition of the Grignard, reaction was stirred at -60 ^{o}C for 15 min then slowly warmed to room temperature. The mixture was stirred at rt overnight followed by quenching with 10% NH_4OH in sat. $NH_4Cl_{(aq)}$ (5 mL), and stirring for 40 min. Extraction with acetone (3 x 40 mL) followed by drying over $MgSO_4$, filtration, and solvent removed under reduced pressure gave a crude product. Purification by column chromatography with 5% EtOAc in hexanes, eluent. Gained oil (33.0 mg, 57%).^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 4.62-4.64 (m, 1H), 3.25-3.28 (m, 1H), 2.50-2.40 (m, 2H), 2.34-2.27 (m, 2H), 0.93 (s, 9H), 0.873-0.869 (m, 1H), 0.02 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, ppm): δ 208.2, 80.9, 57.4, 74.2, 33.2, 27.0, 19.7,0.49.



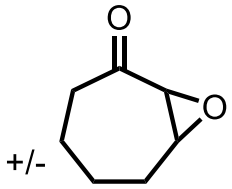
(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-ethylcyclopentanone (3.16)

The procedure was performed same as for **3.17**, using **3.7** (0.132 mmol, 39.9 g) and ethyl magnesium bromide (0.53 mmol, 0.34 mL in ether). Oil (19.0 mg, 58%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 3.71-3.72 (m, 1H), 2.85-2.73 (m, 1H), 2.44-2.22 (m, 2H), 1.95-1.80 (m, 2H), 1.48-1.39 (m, 2H), 1.01- 0.93 (m, 3H), 0.06 (s, 9H), -0.016 (s, 3H), -0.015 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, ppm): δ 212.6, 72.3, 41.1, 37.0, 32.7, 25.7, 25.4, 25.14 18.0, 11.6, -4.93, -4.87.



(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-isopropylcyclopentanone (3.18)

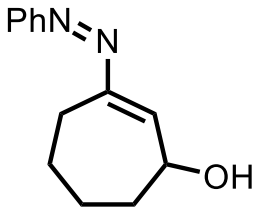
The procedure was performed same as for **3.17**, using **3.7** (0.105 mmol, 31.7 mg) and isopropyl magnesium chloride (0.42 mmol, 0.21 mL in ether). Brown oil (16.0 mg, 60%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 3.81-3.86 (m, 1H), 2.88-2.86 (m, 1H), 2.50-2.40 (m, 2H), 2.02-1.92 (m, 2H), 1.82-1.81 (m, 1H), 0.930 (d, J=7.2 Hz, 6H), 0.812 (s, 9H), -0.017 (s, 3H), -0.016 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 212.1, 72.30, 42.1, 37.4, 31.7, 28.7 23.8, 19.9 -4.91, -4.88.



2,3-epoxycycloheptanone (3.6)

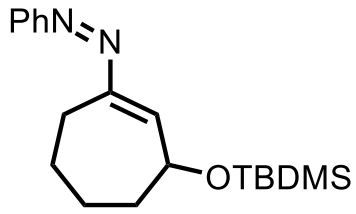
2-Cyclohepten-1-one (9.69 mmol, 1.1 mL) was added to MeOH (20 mL) in a 100 mL round bottom flask equipped with a stir bar, and rubber septum. The colorless solution was subsequently cooled to 0^{o} C using an ice bath and aqueous NaOH (0.88 mL of 20% w/v) was then added dropwise and temperature maintained at 0 ^{o}C. The reaction solution was warmed to room temperature and stirred for 2 h. The reaction was quenched with water (5 mL) followed by extraction with dichloromethane (4 x 20 mL). The combined organic was then dried over $MgSO_4$ filtered, and solvent removed under reduced pressure using a rotovap. To further

remove any water, the product was placed into a vial which was placed in a chamber half filled with drierite under high vacuum for 30 min. Obtained colorless oil (0.750g, 61%). This compound is known, and its reported spectra matches with that reported in literature.[10]



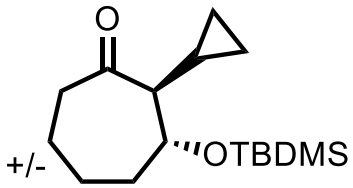
(*E*)-3-(phenyldiazenyl)cyclohept-2-enol (3.12)

In a 25 mL round bottom flask **3.6** (3.23 mmol, 0.41 g) was dissolved in CH_2Cl_2 (1.5 mL) followed by addition of phenyl hydrazine (3.6 mmol, 0.35 mL). The mixture was stirred overnight at r.t. Solvent was removed under reduced pressure and the red crude solid was purified using silica column chromatography using 5% EtOAc in hexanes eluent. Red oil (0.87g, 60%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 7.77 (d, *J*=8.0 Hz, 2H), 7.47-7.45 (m, 2H), 7.40-7.37 (m, 1H), 6.96 (s, 1H), 4.74 (d, *J* =10.0 Hz, 1H), 3.27 (dd, *J* =6.8, 1H), 2.18-2.11 (m, 1H), 2.04-1.99 (m, 1H), 1.94-1.86 (m, 1H), 1.84-1.65 (m, 4H), 0.94 (s, 9H), 0.13 (s, 3H), 0.02 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, ppm): δ 155.6, 148.1, 129.1, 127.1, 120.6, 69.6 34.7, 25.5, 23.4, 22.4.



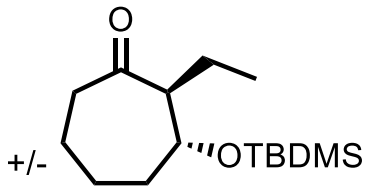
(*E*)-1-(3-((tert-butyldimethylsilyl)oxy)cyclohept-1-en-1-yl)-2-phenyldiazene (3.9)

Compound **3.12** (5.95 mmol, 1.29 g) was dissolved in CH_2Cl_2 (20 mL) in a 50 mL round bottom flask equipped with a stir bar. Imidazole (14.9 mmol, 1.01 g) was added, followed by TBDMSCl (7.14 mmol, 1.08 g). The reaction was stirred at room temperature under Ar for 4 h. Subsequently it was diluted with water (10 mL), and stirred let mix for 10 min. Reaction mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were then washed with sat. $NaCl_{(aq)}$ (40 mL), dried over $MgSO_4$ filtered, and solvent was removed under reduced pressure. Purification by silica column chromatography using 25% EtOAc in hexanes eluent. Red oil (1.25g, 64%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 7.77 (d, *J*=8.0 Hz, 2H), 7.49-7.45 (m, 2H), 7.40-7.37 (m, 1H), 6.96 (s, 1H), 4.74 (d, *J*=10.0 Hz, 1H), 3.27 (dd, *J*=6.8 Hz, 1H), 2.18-2.11 (m, 1H), 2.04-1.99 (m, 1H), 1.94-1.86 (m, 1H), 1.84-1.65 (m, 4H), 0.94 (s, 9H), 0.13 (s, 3H), 0.02 (s, 3H) ; ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, ppm): δ 155.2, 150.8, 150.5, 128.4, 127.3, 120.8, 70.5, 35.1, 26.1, 24.3, 24.1, 23.5, 22.1, 16.6, -4.66.



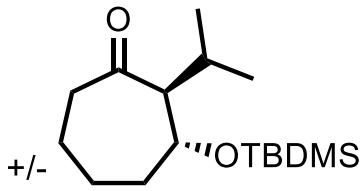
(trans)-3-((tert-butyldimethylsilyl)oxy)-2-cyclopropylcycloheptanone(3.15)

Compound **3.9** (0.234 mmol, 77.3 mg) was dissolved in THF (0.4 mL) inside a flame dried 10 mL round bottom flask equipped with a stir bar. The solution was cooled to -65 ^{o}C using an immersion cooler. In a separate flame-dried round bottom flask was placed cyclopropyl magnesium chloride (0.94 mmol, 1.2 mL in ether) diluted with THF (0.8 ml). Grignard reagent is titrated with 2-hydroxybenzaldehyde phenyl hydrazone before use. Diluted Grignard solution was added to the azoalkene solution via syringe over ~ 15 min. After addition of the Grignard reaction was stirred at -60 ^{o} C for 15 min then slowly warmed to r.t. The mixture was stirred at rt overnight followed by quenching with 10% NH_4OH in sat. $NH_4Cl_{(aq)}$ (5 mL) and stirring for 40 min. Extraction with acetone (3 x40 mL) followed by drying over $MgSO_4$ filtration, and solvent removed under reduced pressure gave the crude product. Purification by column chromatography with 5% EtOAc in hexanes eluent. Red-brown oil (32.0 mg, 48%) was obtained.^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 3.91-3.83 (m, 1H), 2.60-2.49 (m, 1H), 2.40-2.26 (m, 2H), 1.88-1.76 (m, 4H), 1.57-1.42 (m, 2H), 1.30-1.29 (m, 1H), 0.89 (s, 9H), 0.860-0.848 (m, 4H), -0.01 (s, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 210.3, 74.6, 41.1, 38.8, 31.1, 27.9, 25.7, 21.7, 20.8, 18.1, 17.0, 3.8, -4.5.



(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-ethylcycloheptanone (3.17)

The procedure was performed same as for **3.15**, using **3.9** (0.234 mmol, 77.3 mg) and ethyl magnesium bromide (0.94 mmol, 0.59 mL in ether). Brown oil (26.0 mg, 42%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 3.75-3.70 (m, 1H), 2.58-2.41 (m, 2H), 1.93-1.79 (m, 2H), 1.93-1.92 (m, 1H), 1.77-1.62 (m, 4H), 1.56 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H) ; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 210.2, 74.7, 51.5, 38.8, 31.0, 27.9, 25.7, 25.8, 25.8, 21.3, 18.1, 12.1, -4.5.



(*trans*)-3-((tert-butyldimethylsilyl)oxy)-2-isopropylcycloheptanone (3.20)

The procedure was performed same as for **3.15**, using **3.9** (0.234 mmol, 77.0 mg) and isopropyl magnesium chloride (0.936 mmol, 0.62 mL in ether). Oil (22.0 mg, 33%) was obtained. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm): 4.01-3.98 (m, 1H), 2.82-2.77 (m, 1H), 2.52-2.43 (m, 1H), 2.38-2.30 (m, 1H), 1.83-1.56 (m, 5H), 1.49-1.34 (m, 2H), 0.91 (s, 9H), -0.013 (s, 3H), -0.011 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz, ppm): δ 210.1, 74.6, 52.6, 38.8, 31.0, 29.4, 27.9, 25.7, 25.9, 21.1, 23.2, 20.2, 18.1, -4.6.

3.6 Bibliography

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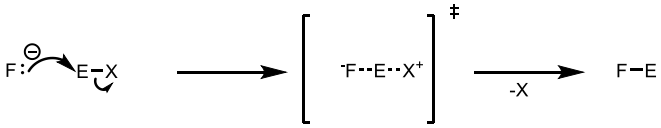
CHAPTER 4

ELECTROPHILIC MONOFLUORINATION OF ORGANOMETALLIC REAGENTS

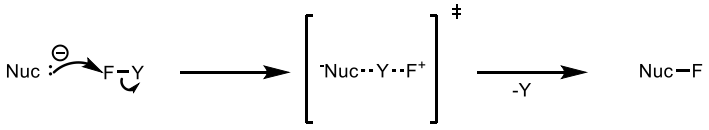
4.1 Introduction

Monofluorination of organic molecules has a longstanding history in synthetic chemistry.[1] Monofluorinated organics have found use in agrochemistry and pharmaceutical chemistry.[2] However, while there has been an emergence of novel synthetic fluorination techniques, a general method for organoelement electrophilic fluorination with high functional group tolerance still remains elusive. Fluorination synthetic strategies that have been developed over the years can be categorized into three types depending on the fluorinating reagent: anionic, and cationic.[1] However, radical fluoride abstraction strategies have been developed and will be discussed further in Chapter 5. New research has shed mechanistic insight into the role of single electron transfer on C-F bond formation.[1,56] Anionic or nucleophilic fluorination occurs when the fluorine acts as a nucleophile (Scheme 4.1). Many reagents have been developed over the years allow the controlled release of anionic fluorine to facilitate monofluorination.[3] Cationic fluorination or electrophilic fluorination occurs when the fluorine acts as an electrophile (Scheme 4.2). This is possible when fluorine is attached to an electronegative atom such as oxygen or nitrogen.

Scheme 4.1 Nucleophilic Fluorination



Scheme 4.2 Electrophilic Fluorination

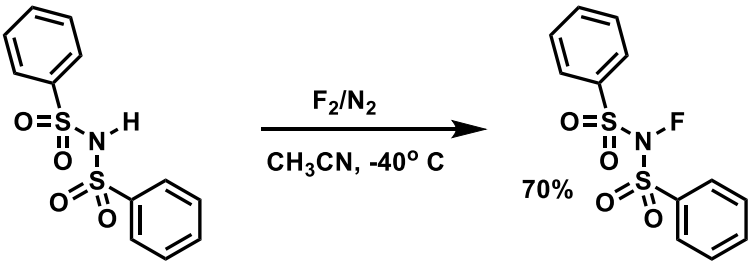


This chapter will focus on reviewing electrophilic fluorination of organometallic reagents towards monofluoro-organic compound formation. Although molecular fluorine is the simplest source of fluorine, its high toxicity and high boiling point makes it operationally dangerous to use.[4] While molecular fluorine is effective, it may results in low C-F bond formation selectivity due to uncontrollable radical intermediates being formed under the reaction conditions.[1] Another simple yet toxic fluorinating agent includes molecular HF. The use of HF has found widespread use in perfluorination of polymers in the Simmons[5] reaction and it has been used as stabilized pyridine*HF or $KHSO_4$*HF. However, such reagents pose many operational problems along with very limited substrate scope towards nucleophilic fluorination and causing non- selective C-F bond formation.[6] Due to the increasing demand of fluorinating agents that are more chemo- and regioselective in addition to being safe and stable, much attention has been placed on electrophilic fluorinating agents possessing the N-F moiety. Use of inorganic compounds such as trifluoroamine *N*-oxide, dinitrogen difluoride, fluorine nitrate, and tetrafluoroammonium or fluorodiazonium salts has been reviewed in literature.[7-12] Other inorganic fluorides such as XeF_2 and CsF have been used for electrophilic and nucleophilic fluorination as well.[13, 56]

Before the use of fluorinating agents possessing the N-F moiety chemists used reagents possessing O-F functionality. Examples involve use of acyl hypofluorites and sulfonyl hypofluorites. However, these compounds are operationally difficult to use and give poor

fluorination site selectivity.[14,15] Consequently, chemists shifted to using fluorinating agents possessing the N-F moiety as a viable alternative that is safer to handle and operationally simple to use. There are two classes of N-F fluorinating reagents: neutral (R_2NF) and quaternary ammonium N-F reagents ($R_3N^+F\ A^-$). Based on the electronic density on the nitrogen, either nucleophilic or electrophilic fluorination can be achieved using N-F reagents. For neutral N-F reagents reactivity can be increased by adjacent carbonyl or sulfonyl groups, providing a more electropositive F^+ donor. A notable example is *N*-fluorobenzenesulfonimide (NFSI) developed by Differding and co-workers (Scheme 4.3).[16] These reagents were originally developed as an alternative to *N*-fluorosultams which suffered from being less reactive with respect to enol ethers and aromatic compounds.[16] In addition to its higher reactivity with enolates, NFSI directly fluorinates monosubstituted aromatics bearing an EDG without the use of base. It has also found recent use in metal catalyzed amination of aromatics.[17] Other N-F reagents that are still used are *N*-fluoropyridinium salts developed by Umemoto and co-workers,[4] *N*-fluorobis[(trifluoromethyl)sulfonyl]imide discovered by DesMarteau[18,19] (not commercially available), and SelectFluor ® originally developed by Banks.[20,21]

Scheme 4.3 Preparation of NFSI



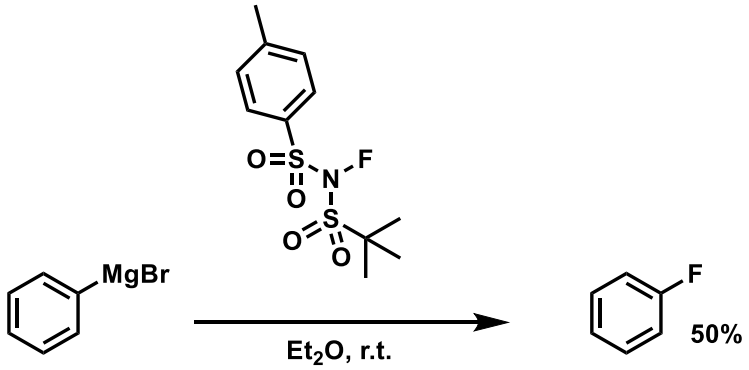
This chapter will discuss the use of these reagents in the electrophilic fluorination of different organometallic species such as Grignards, organolithiums, and organotin reagents. In addition to these metals, silver and copper salts have found utility as either oxidants or co-

catalysts to help mediate such transformations.[22] However, there has been a significant lack of development of electrophilic monofluorination of organozinc reagents up until our work.

4.2 Electrophilic Fluorination of Grignard Reagents and Organolithiums

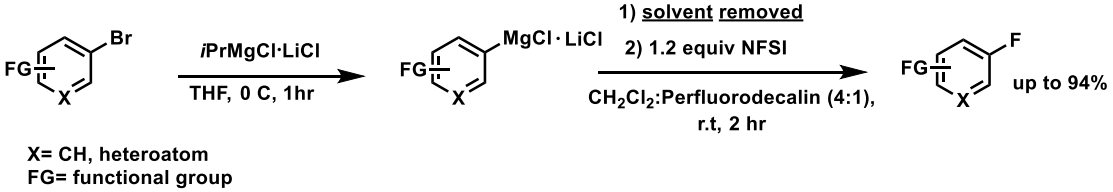
One of the earliest direct electrophilic fluorinations of a Grignard reagent was reported by Schlosser in 1977.[23] He obtained 37% yield of benzyl fluoride by reacting benzylmagnesium chloride with perchloryl fluoride ($FClO_3$). As mentioned previously, perchloryl fluoride is not widely used in modern times due to being operationally difficult to handle, explosive, and providing low yields of the desired mono-fluorinated product. Another early attempt at electrophilic fluorination of Grignard reagents was made by Barnette in 1984, where he reacted PhMgBr with an *N*-fluoro-*N*-alkylsulfonamide derivative to obtain the 1-fluoro benzene in 50% yield (Scheme 4.4).[24] The yield is higher than that reported by Schlosser. Several years later, Umemoto showed that subjecting PhMgBr to *N*-fluoro 2,4, 6 trimethylpyridinium triflate at 0° C gave a 58% yield of fluorobenzene.[4,25] Most researchers have found improved yields of electrophilic fluorination by running reaction at 0 °C for Grignard reagents rather than at room temperature.[26,27]

Scheme 4.4 Barnette's Electrophilic Fluorination of a Grignard Reagent



Knochel and Beller were able to independently develop high yielding electrophilic fluorination of aryl Grignard reagents.[28-31] These are the first examples of high yielding electrophilic fluorination of Grignard reagents. Knochel and co-workers were able to perform electrophilic fluorination of aryl and pyridyl-derived Grignard reagents with yields up to 94% using NFSI as F^+ source (Scheme 4.5). They found that replacing THF with CH_2Cl_2:perfluorodecalin (4:1) gave significantly higher yields of the desired aryl monofluoride.[28] The use of the perfluorodecaline suppresses the radical pathway that would generate the undesired hydrocarbon byproduct. Knochel and co-workers provided a follow up paper on a practical preparation of functionalized aromatic and heteroaroatic fluorides from aryl Grignards using the same conditions.[29]

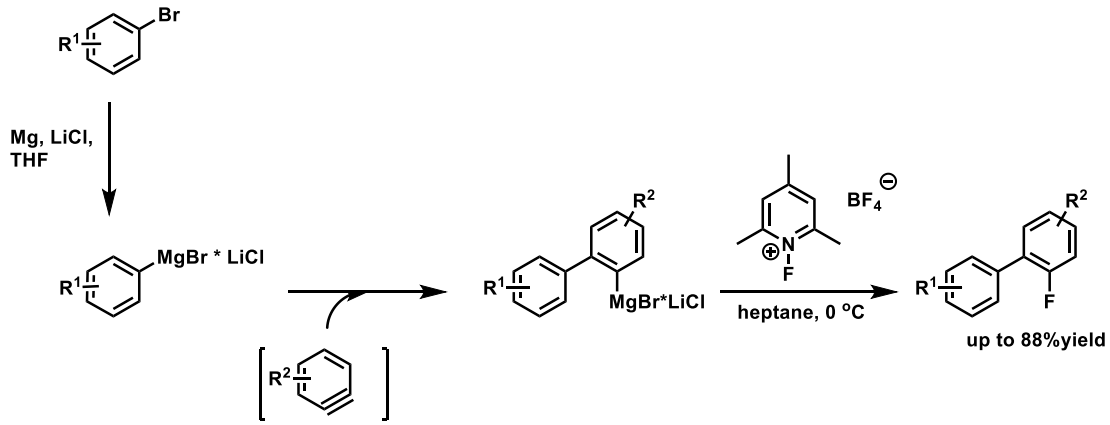
Scheme 4.5 Knochel Electrophilic Fluorination of Grignard Reagents



Beller's group offered a different approach towards the electrophilic fluorination of substituted aryl Grignard reagents. They found that heptane and $CH_3OC_4F_9$ worked equally well and these solvents were used to replace THF. As with Knochel reactions, Beller's group discovered that yields improved when THF is completely removed. Beller's group used 2,4,6-trimethylpyridinium fluoride tetrafluoroborate as the F^+ source.[30] They were able to obtain up to 84% yield of the desired mono-fluorinated aryl products. The group later expanded their synthetic approach to allow a tandem reaction *in situ* preparation of bi-aryl Grignards before fluorination (Scheme 4.6).[31] The *in situ* formed bi-aryl Grignard was obtained by reacting the pre-formed aryl Grignard with benzyne followed by electrophilic fluorination with 2,4,6

trimethylprydinium fluoride tetrafluoroborate. Electrophilic fluorination of alkyl Grignards has been reported by Umemoto and co-workers that show 77% isolated yield of 2-fluoroadamantane by fluorinating 2-adamante Grignard with a fluoro-*N*-pyridinium salt.[25]

Scheme 4.6 Beller's Modified Electrophilic Fluorination of Grignard Reagents

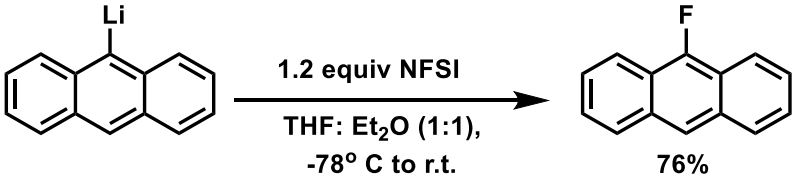


While the fluorination of Grignard reagents has been explored, these reactions are intrinsically limited by substrates that can be employed. No substrates bearing any carbonyl moiety can be used due to nucleophilic attack by the Grignard reagent. In addition to a lack of functional group tolerance, the use of Grignard reagents suffers from lower regioselectivity. If other halogenated functional groups are present in the molecule, undesired side reactions may occur. There is also an issue of site selective fluorination of the Grignard reagent.

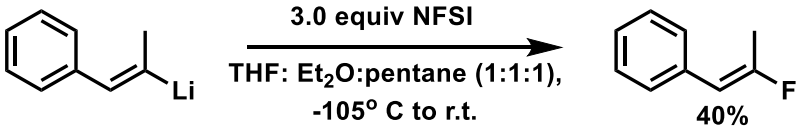
Organolithium reactivity is analogous to that of Grignard reagents, with the exception that they have a narrower substrate scope. Organolithium reagents have a vast synthetic history of participating in electrophilic fluorination to form monofluorinated compounds. When Differding developed NFSI, one of the first reagents used to screen its reactivity were organolithium compounds.[16] When reacting a slight excess of NFSI with anthracenyl lithium at

-78 ^{o}C, the desired monofluoride was obtained in 76% yield (Scheme 4.7). However, vinyl lithiated species gave only 40% yield of the desired monofluoride (Scheme 4.8).

Scheme 4.7 Electrophilic Fluorination of Aryl-Lithium with NFSI

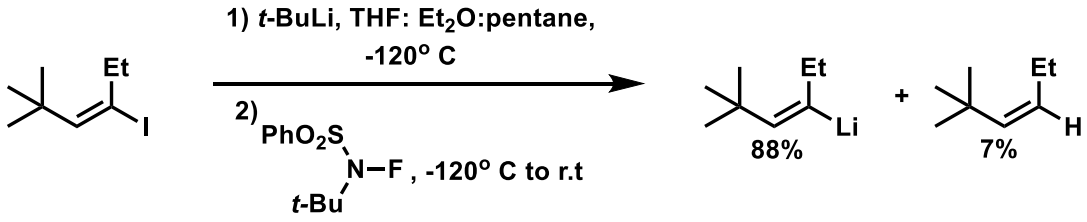


Scheme 4.8 Electrophilic Fluorination of Vinyl Lithium with NFSI



Shwartz and his group demonstrated direct electrophilic fluorination of organolithium reagents using an *N*-fluoro-*N*-alkylsulfonamide-derived fluorinated agent to obtain the monofluorinated alkenes in high yields with retention of configuration (Scheme 4.9).[32-34] Alkenyl iodides served as the starting materials. Lithium-iodide exchange to form the organolithium *in situ* was followed by electrophilic fluorination. More examples of electrophilic fluorination of organolithiums are described in Cahard's and Baudoux chapter in Organic Reactions.[1]

Scheme 4.9 Improved Electrophilic Fluorination of Vinyl lithium



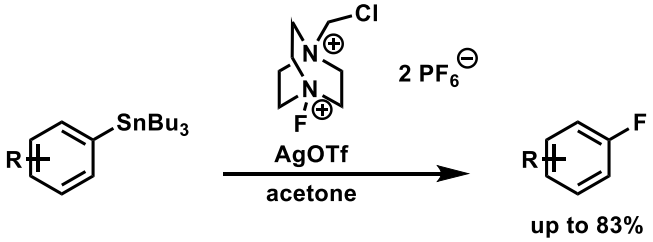
Organolithiums are not as popular as Grignard reagents in fluorination reactions. This is perhaps due to their higher reactivity and thus reactions are more difficult to control. Organolithium unlike Grignard reagents have a more polarized C-M bond thus in addition to reacting as nucleophiles they can also react as bases. Grignard reagents can also act as bases under certain conditions, but this reactivity is less pronounced than that of organolithiums. This also leads to the narrow substrate scope offered by organolithiums due to their high reactivity. Also, some organolithium reagents might be prone to unwanted lithium-halogen exchange if other halogenated functionalities are present elsewhere in molecule.

4.3 Electrophilic Fluorination of Organostannates

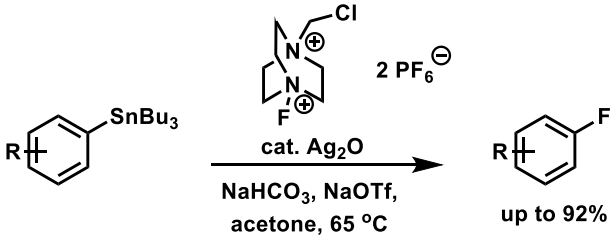
In the pursuit of a generalized synthetic methodology towards electrophilic monofluorination, researchers have used organostannates as viable reagents. Stannanes can be synthesized by transmetallation from Grignard or organoaluminum reagents or they can be obtained directly by reacting Sn (0) with alkyl halides or other alkyl electrophiles.[35] A lesser used organostannate, alkylcarbastannatrane can be prepared by reacting alkyl metal nucleophile with carbastannatrane chloride or by using alkyl mesylate reaction with lithium carbastannatrane.[36] Alkylcarbastannatranes have also been prepared via transmetallation of alkylzincs or zincated carbastannatranes if sensitive functional groups are present in the starting material.[36] Organostannates in general are tolerant to a wide range of functional groups including ketones, amides, esters, boronic ester, and others.[35] However, organotin is problematic to install on 3^{o} carbons. There has been tremendous advancement within the field recently for the electrophilic fluorination of both aryl- and alkyl- stannates.

Ritter has shown direct electrophilic fluorination of aryl stannates using Ag(I) and Selectfluor ® (Scheme 4.10).[36] The procedure is operationally simple and tolerates phenols, amine oxides, and has been exploited to modify biologically active molecules. Ritter's group has since improved on their previous method by using Ag_2O to mediate the reaction (Scheme 4.11).[37] They have also developed a Pd(IV) synthetic methodology that shows promise in electrophilic ^{18}F transformations.[38]

Scheme 4.10 Ritter's Electrophilic Fluorination of Aryltins

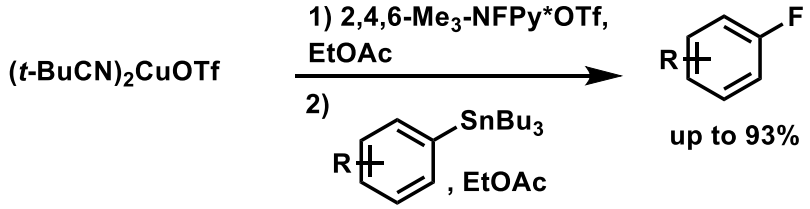


Scheme 4.11 Ritter's Modifed Fluorination of Aryltins



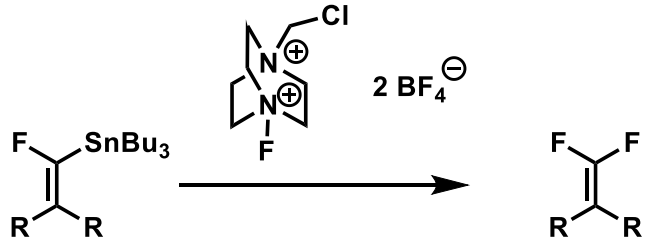
Sanford and co-workers employed Cu(I) mediated fluorination of arylstannanes using 2,4,6- trimethyl *N*-fluoropyridinium triflate as the fluorinating agent (Scheme 4.12).[39] They reported moderate to good NMR yields of the mono-fluorinated products under mild reaction conditions. Sanford's group also developed electrophilic and nucleophilic ^{18}F fluorination of organostannanes in good yields.[40,41] However, like Ritter they do not show the utility of their synthetic methodologies towards monofluorination of alkanes. In addition to aryl stannanes, vinyl and alkyl stannanes have also been used under electrophilic fluorination conditions.

Scheme 4.12 Sanford's Electrophilic Fluorination of Arylstannanes

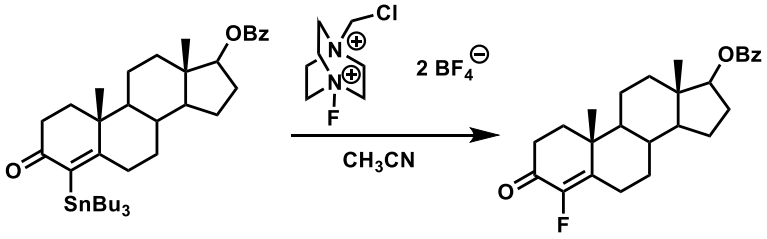


McCarthy's and Widdowson have independently developed electrophilic fluorination of vinyl stannanes using Selectfluor ® reagent.[42,43] By employing McCarthy's method, fluorovinyl stannanes can be made directly from the ketone and subsequently fluorinated to provide geminal difluorides (Scheme 4.13).[44] McCarthy also showed one entry of monofluorination of a vinyl stannane. Although good yields were reported, researchers only employed terminal olefins and would observe mixture of monofluorinated olefins in the crude reaction, leading them to suspect that Selectfluor ® may not react regioselectively. Widdowson, on the other hand, was able to expand the substrate scope towards electrophilic fluorination of vinyl steroid (Scheme 4.14) using Selectfluor ®. However, Widdowson only showed one example of such reaction and monofluorinated steroid was obtained in relatively low yield of 52%.

Scheme 4.13 McCarthy's Electrophilic Fluorination of Vinyl Stannates

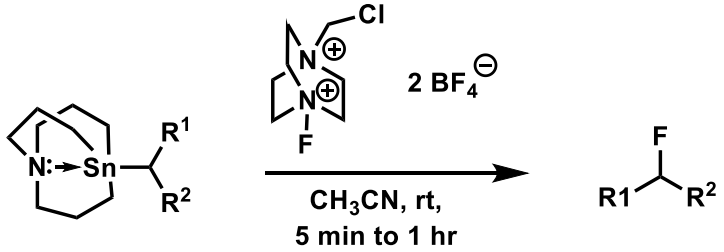


Scheme 4.14 Electrophilic Fluorination of a Steroid



Direct electrophilic fluorination of enantioenriched alkylcarbastannatrane reagents have been reported by Biscoe and co-workers (Scheme 4.15).[45] They have found that alkyltin nucleophiles exhibit no activity towards fluorination in the absence of a carbastannatrane backbone. In literature, similar structures were used in transmetallation of Sn to Pd.[57] It was found that the transannular N-Sn interaction in the carbastannatrane backbone activates the Sn-C bond thus facilitating the transfer of the alkyl group. This bond would otherwise be deactivated towards transmetallation. Biscoe applied this observation towards electrophilic fluorination by using Selectfluor ®. Their methodology works with primary and secondary alkyl groups bearing unique functional groups such as alcohols, esters, and silyl enol ethers, while previous chemistry is not tolerant to these functionalities. The desired monofluorinated species were obtained in good yields and enantioselectively via stereoinvertive mechanism.

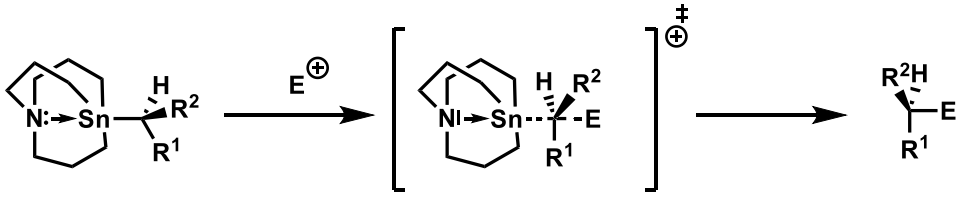
Scheme 4.15 Electrophilic Fluorination of Alkylcarbastannatranes



Biscoe and co-workers proposed that the reaction proceeds via stereoinvertive S_E2 polar mechanism (Scheme 4.16), which is similar to previously reported electrophilic enantioselective halogenation.[46] Their data show that the enantioenriched

alkylcarbastannatranes, undergo net inversion under the reaction conditions. Up to 98% enantiospecificity in formation of the mono-fluorinated product is obtained. While the methodology is effective, there is still a narrow substrate scope that is employed using alkylcarbastannatranes. Using Biscoe's method, it is impossible to form fluorinated 3° alkanes. In addition, no allylic or vinyl fluorides were synthesized using their method. The synthesis of these alkylcarbastannatranes can be operationally time consuming-and may have stability issues for more complex molecules bearing multiple functionalities. Furthermore, tin compounds are often quite toxic.

Scheme 4.16 Proposed Mechanism of Electrophilic Fluorination of Alkylcarbastannatranes

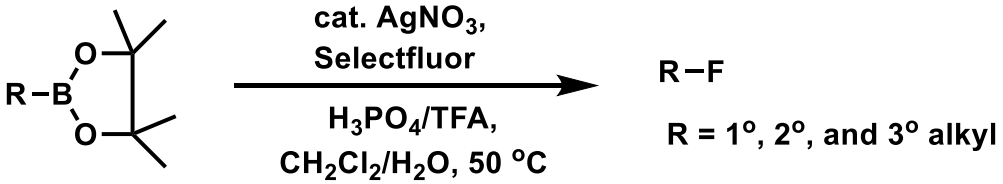


4.4 Electrophilic Fluorination of Miscellaneous Compounds

Direct electrophilic and nucleophilic fluorination of organoboron compounds have been developed.[52] Li and co-workers reported direct electrophilic fluorination of boronic acids and pinacol esters using a silver catalyzed fluorination with Selectfluor ® as the fluorine source (Scheme 4.17).[53] These reactions also work in aqueous media. Limitations of this approach include solubility issues, difficulty of synthesizing some of the boronic acids or pinacol esters, and stability issues as acid conditions are used. Preparation of alkyl monofluorides from carboxylic acids have also been reported in literature. However, these reaction conditions

require multiple steps to prepare the starting material and reproducibility of yields may be an issue.[54,22]

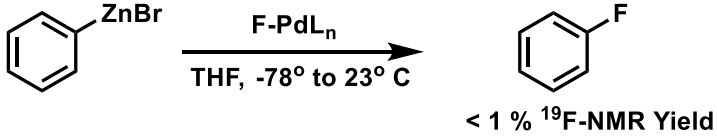
Scheme 4.17 Electrophilic Fluorination of Alkyl Pinacol Esters



4.5 Fluorination of Organozinc Reagents

The direct electrophilic monofluorination of alkyl organozincs has not been reported to our knowledge. To date, the only reaction was reported by Ritter and co-workers where they attempted to fluorinated phenyl zinc bromide with their Pd(IV) reagent (Scheme 4.18).[47] They reported detection of 1-fluorobenzene by fluorine NMR.

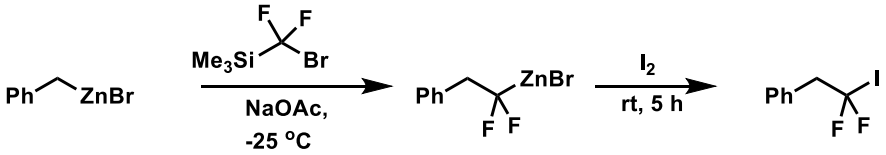
Scheme 4.18 Electrophilic Fluorination of Arylzinc Reagent



Organozinc reagents have been employed in formation of geminal difluorides.[48] However, this was accomplished via a pre-fluorinated carbene that inserts into the alkyl zinc Halogenation of the organozinc gives the final product (Scheme 4.19). Zinc has also been employed as a catalyst towards fluorcyclization of alkenes.[49] However this, like the carbene reaction, is not electrophilic fluorination nor does it allow for direct fluorination of the alkyl

zinc. Other methods towards fluorinated alkyl zincs use pre-formed fluorinated species reacting with Zn^0 to give fluorinated alkyl zincs.[50,51]

Scheme 4.19 Reaction of Difluorocarbene with Organozinc



Alkyl zinc reagents are particularly useful since these are easy to make and possess wide functional group tolerance that is only rivaled by organotin reagents. Furthermore, alkyl zincs are non-toxic. Additionally, they are operationally simple and safe to use compared with pyrophoric Grignard reagents or organolithiums. If direct electrophilic fluorination of alkyl zincs can be employed, for the first time a general synthetic methodology towards mono-fluorinated alkanes can be achieved. Like alkyltins, organozinc reagents have the tremendous potential to undergo site selective monofluorination, providing products in high regioselectivity.

4.6 Bibliography

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CHAPTER 5

ELECTROPHILIC MONOFLUORINATION OF ORGANOZINC REAGENTS

5.1 Introduction

Most molecules useful as drugs or materials are polyfunctional compounds. Consequently, their synthesis requires selective and site-specific transformations. From a retrosynthetic standpoint, such highly selective and specific point changes on a polyfunctional molecules are difficult. To overcome these challenges, chemists have developed organometallic compounds with wide functional group tolerance. The caveat here is that these organometallic reagents are unreactive to many organic electrophiles.[1] Organozinc reagents are such compounds that have a wide functional group tolerance but often need another metal to catalyze further reactivity.[2,3] However, they have not been fully explored towards carbon-heteroatom bond formation.[4]

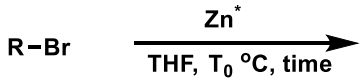
Organozinc reagents are less reactive than Grignard reagents or organolithiums because of the strong covalent nature of the C-Zn bond.[5] As a result, C-Zn bond is relatively inert to many functional groups, with the exception of hydroxy groups and azides. Organozinc reagents can be easily prepared by direct insertion of Zn(0) into an alkyl/aryl halide, or transmetallation of a Zn salt with organolithium, magnesium, or mercuric species.[1] Dialkylzinc compounds will not be discussed in this chapter.[6] As discussed in Chapter 4, electrophilic fluorination of organozinc species has not been explored until now. We are interested in organozinc reagents for the following reasons: they are easy to prepare, they possess good functional group tolerance, and unlike organotin compounds, they are non-toxic. Chapter 5 will discuss preparation of active metallic zinc, preparation of the organozinc reagent, and development of electrophilic fluorination of organozinc compounds using commercially available and inexpensive NFSI.

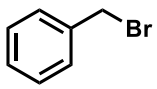
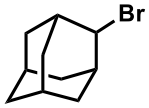
5.2 Results

5.2.1 Preparation of Organozinc Reagents

A streamlined synthetic approach for the preparation of organozinc reagents is ideal as it makes the overall process operationally simple and less time consuming. We chose to synthesize organozinc compounds via zinc metal directly inserting into commercially available or easily prepared alkyl halides. To perform zinc insertion into the C-X bond (X= Cl, Br or I) the zinc metal needs to be properly activated. We explored different ways of activating metal zinc. The first method was activating Zn dust with 2% $HCl_{(aq)}$ followed by washing with different solvents. This procedure removes oxides from the Zn surface, however, the Zn cannot be stirred in the dilute acid for long periods of time or risk converting to $ZnCl_{2(aq)}$.[7] This activated Zn dust (Zn^*) successfully reacted with benzylic and secondary alkyl bromides (Table 5.1).

Table 5.1 Organozinc Preparation with Acid Activated Zn Dust

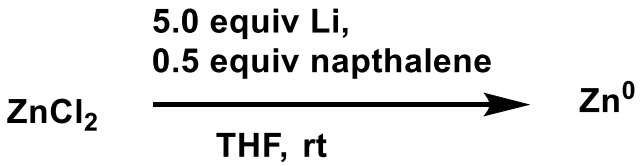


R–Br	T_0 °C	time	R–ZnBr[a]
	60	40 min	0.4 M
	86	24 hr	0.1 M

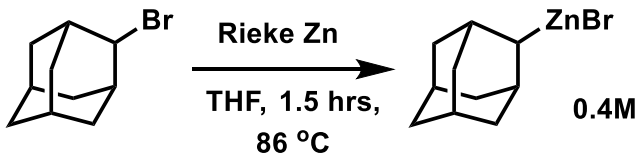
[a]Organozinc compound titrated with I_2

However, the long reaction times and low conversion for secondary and tertiary adamantane halides made it a less satisfactory method. Rieke zinc was found to be a viable alternative. Discovered in 1996, the formation of Rieke zinc occurs via the reduction of $ZnCl_2$ by Li and catalytic amounts of naphthalene to produce a black Zn(0) powder (Scheme 5.1).[8,9] This slurry of highly reactive Zn(0) can be used immediately towards direct insertion in an alkyl halide. Preparation of organozinc reagents via transmetallation was not used as we would encounter limited substrate scope since Grignard reagents or organolithium are not functional group tolerant.[10] Rieke Zinc gave high yield for 2-bromo-adamantane zincation (Scheme 5.2). Due to the reduced reaction time and improved conversion, Rieke procedure was used to prepare activated zinc.

Scheme 5.1 Preparation of Rieke Zinc



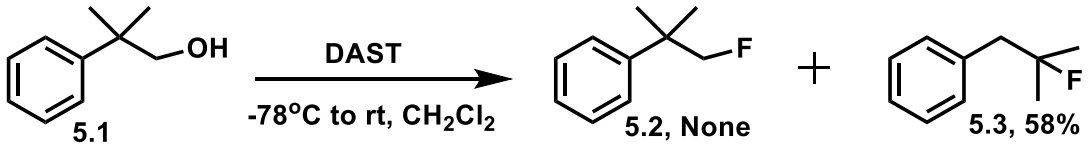
Scheme 5.2 Organozinc Preparation Using Rieke Zinc



5.2.2 Electrophilic Fluorination of Organozinc Reagents

Having a streamlined procedure for the preparation of organozinc compounds in hand, we explored electrophilic fluorination of these reagents. The synthesis of organomonofluorides is important, as 30% of agrochemicals contain a C-F bond.[11] While there have been various synthetic strategies used to make hydrofluorocarbons using nucleophilic and electrophilic reagents such as DAST, TBAF, pyridinium, or Selectfluor ®, many of these approaches are limited by substrate scope and undesired side reactions.[12-14] Primary alcohols may be prone to β-elimination under nucleophilic fluorination conditions using DAST. Certain short-chain phenyl alcohols are prone to undesired rearrangements under nucleophilic fluorination conditions (Scheme 5.3).

Scheme 5.3 Undesired Rearrangement Under Nucleophilic Fluorination

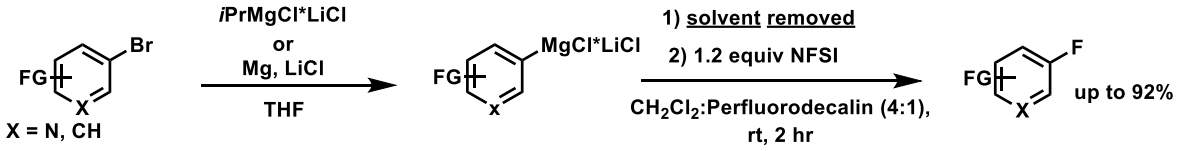


Nucleophilic fluorination of alkyl halides using TBAF is effective, but it is limited by substrate scope as tertiary alkyl halides are unreactive since the reaction proceeds via an S_N2 mechanism. Alkyltin reagents, while effective, are usually made in several steps, are toxic, and cannot be used for fluorination of tertiary compounds. As discussed in Chapter 4, the only known reported fluorination of phenyl zinc reported by Ritter in 2014 gave trace yields of the desired fluorinated compound.[15]

Our attention was drawn to observations made by Knochel and co-workers. They found that in reaction of aryl Grignards with NFSI low yields of fluorinated compounds were obtained.[16] They proposed that the electrophilic fluorination of Grignard reagents proceeds via

electrophilic fluorination, but a competing SET reaction occurs causing undesired decomposition of the active Grignard reagent. To mitigate this, they found that complete removal and replacement of THF with CH_2Cl_2:perfluorodecalin mixture (4:1) allowed for significantly improved fluorination yields (Scheme 5.4).

Scheme 5.4 Electrophilic Fluorination of Grignard Reagent



Considering the results and techniques employed by Ritter's and Knochel's groups, we initially screened electrophilic fluorination of benzyl zinc (Table 5.2).[15,16] In **entry 1** of Table 5.2, we observed a result similar to Ritter where only a trace of the desired product was formed when THF is present. When using other solvents in addition to THF, such as CH_2Cl_2 and $(CH_2Cl_2)_2$, slightly higher yields of 7% and 12% were observed. In **entry 4**, THF is completely removed and $(CH_2Cl_2)_2$ was used as the solvent for the fluorination step. Benzyl fluoride was obtained in 79% yield. This high yield of benzyl fluoride when THF is absent strongly implies that hydrogen abstraction side reaction is being suppressed. The THF solvent is well known to be prone to hydrogen abstraction under certain conditions.[17,18]

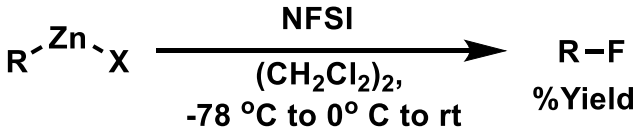
Table 5.2 Solvent Screen: Electrophilic Fluorination of Benzyl Zinc

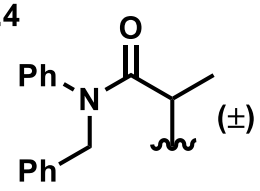
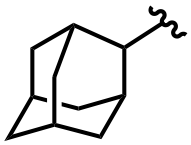
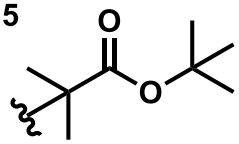
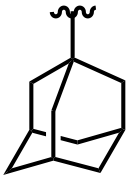
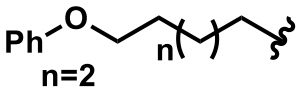
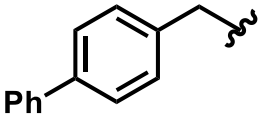
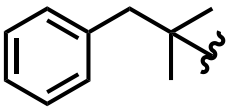
Entry	Solvent	%Yield
1	THF	< 5%
2	CH_2Cl_2 in THF	7%
3	$(CH_2Cl)_2$ in THF	12%
4	[a]$(CH_2Cl)_2$	79%

[a]remove THF from organozinc
[*]internal standard = 1,3,5 trifluorobenzene

We selected NFSI as our reagent of choice as it is relatively inexpensive and commercially available. Other N-F reagents were not explored as NFSI worked well. With the optimized conditions in hand, we performed a substrate screen to showcase the functional group tolerance of our synthetic methodology (Table 5.3). The reaction conditions tolerate 1°, 2°, and 3° alkyl substrates, in addition to ethers, esters, and amides. Compound **5.4** possessing an amide group is fluorinated in 90% yield, without any β-elimination or over-fluorination byproduct. Tertiary substrates **5.5** and **5.3** can be fluorinated in good yields of 70% and 68%, respectively. However, due to its low boiling point, yield of compound **5.5** was calculated based on fluorine NMR. The reaction conditions are also tolerant of long alkyl chains and **5.6** was obtained in 97% yield.

Table 5.3 Electrophilic Fluorination of Organozinc Compounds



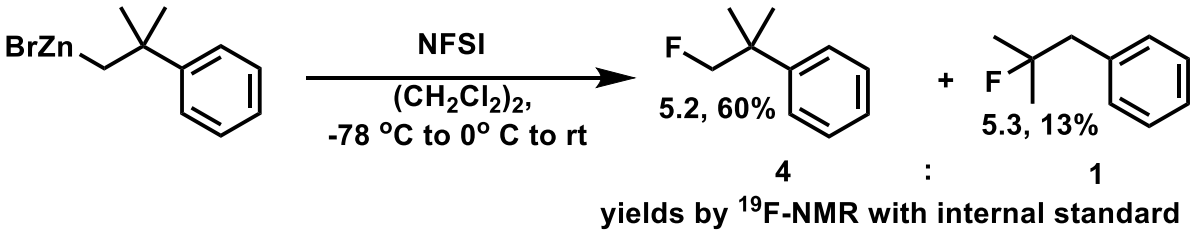
R	% Yield	R	% Yield
5.4 	90%	5.7 	83%
5.5 	70*%	5.8 	84%
5.6 	97%	5.9 	84%
5.3 	68%		

*Determined by ^{19}F-NMR using trifluorotoluene as an internal standard

Caged alkyl substrates such as **5.7** and **5.8** were fluorinated in excellent yields of 83% and 84%. Notably, the formation of the organozinc reagents for adamantane substrates is fast compared to Grignard reagent formation thus reducing overall reaction time. Compound **5.9** was obtained in 84% showing that inductively donating group in a benzylic system is tolerated under the reaction conditions. In testing our reaction conditions with substrates prone to

rearrangements, such as alkyl phenyl moieties, the primary monofluorinated compound **5.2** was observed as the major product (Scheme 5.5). The regioselectivity significantly improved compared with nucleophilic fluorination of the alcohol shown before in Scheme 5.3. Overall, the electrophilic fluorination of organozinc compounds possesses wide functional group tolerance thus making it a good, generalized methodology to prepare alkyl monofluorides.

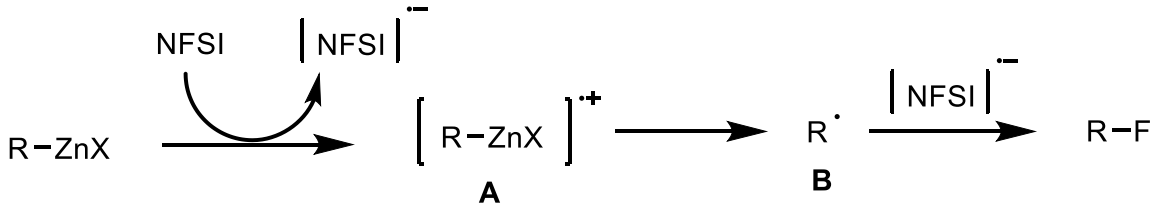
Scheme 5.5 Suppressed Rearrangement Under Electrophilic Fluorination Conditions



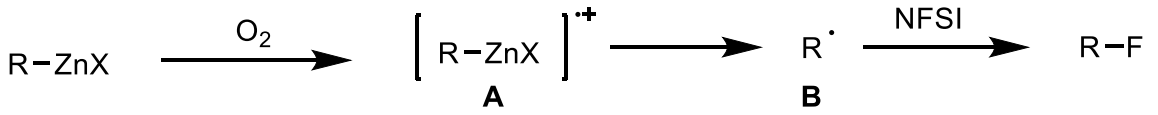
5.3 Discussion

Based on results of our preliminary solvent study, substrate screen and literature findings, we propose that the electrophilic fluorination of organozinc compounds is proceeding via a radical or SET reaction pathway. It has been well precedented that organozinc reagents can undergo radical transformations as suggested by radical clock studies.[19,20] However, organozinc reagents reactions by SET reaction pathway in fluorination has not been reported in the literature to our knowledge. The two possible mechanisms are as follows: first, NFSI can act as radical initiator, or second, oxygen could perform the same role. Both reagents are known to initiate SET of organometallic reagents under certain conditions (Schemes 5.6 and 5.7).[19-21]

Scheme 5.6 Proposed Mechanism of Electrophilic Fluorination with NFSI as Initiator



Scheme 5.7 Proposed Mechanism of Electrophilic Fluorination with Oxygen as Initiator

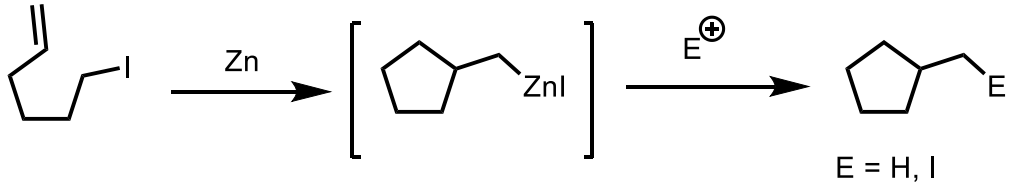


A proposed reaction pathway is illustrated in Scheme 5.6. NFSI has been used as a radical initiator for the sulfoxidation of alkenes and alkynes.[22] Its use in radical reactions has largely focused on amination, aminofluorination, or arene amination.[23-26] Initial removal of one electron from organozinc generates radical cation **A** that transforms to radical **B**. Thereafter, radical B reacts with the anion to form the desired organomonfluoride via fluorine abstraction. The suggested SET pathway (Scheme 5.6) was inspired by proposed mechanism for SET-induced Grignard reagent arylation.[27] NFSI is not well studied as a radical initiator for organometallic reagents which makes the proposed mechanism somewhat less likely. An alternative mechanism can be proposed where oxygen is the radical initiator (Scheme 5.7). It has been documented that trace amounts of oxygen can be radical initiator for organozinc reagents.[19,20] In the proposed mechanism illustrated in Scheme 5.7, oxygen removes one election from organozinc generating cation **A** followed by transformation to radical **B** that can then react with NFSI to produce the organomonofluoride. It is well documented that NFSI can

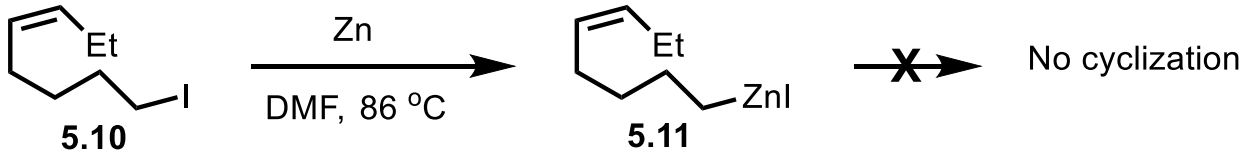
behave as a fluorine transfer agent to alkyl radicals.[21,28] As the calculated BDE of the N-F bond is 63 kcal/mol, it is a great candidate for radical fluorine abstraction.[28,21]

To investigate the reaction mechanism we performed a test for radical intermediate based on the work of Narmant, Meyer, Marek, and Cohen.[19,20] In 1993 Narmant and co-workers described the intramolecular cyclization of alkylzinc iodides followed by electrophilic quench, with H^+ or I^+ at ambient temperature (Scheme 5.8). The stereochemistry of the carbozincation has also been explored.[19] Interestingly, they reported that alkene **5.10** does not cyclize, excluding, long-lived radical intermediacy (Scheme 5.9). This initial finding was further validated several years later by Cohen repeating the same experiment.[19]

Scheme 5.8 Intramolecular Alkylzinc Cyclization



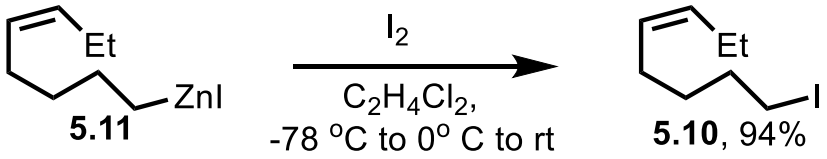
Scheme 5.9 Alkylzinc Formation



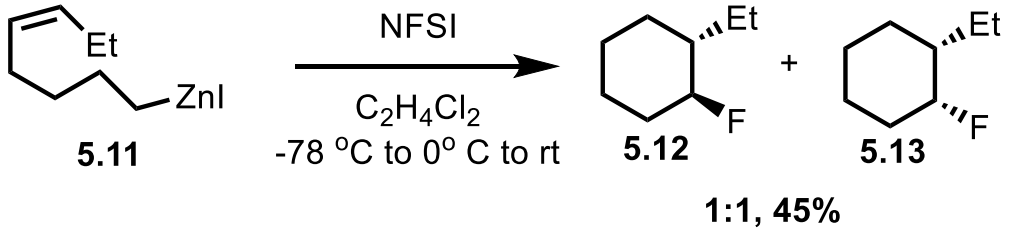
Due to organozinc **5.11** not cyclizing we considered it to be a great candidate for the control experiment to test if electrophilic fluorination of organozinc reagent proceeds via a radical pathway. The preliminary mechanistic study was carried out under our reaction conditions. We used THF solvent to form the organozinc, followed by removal and replacement with $(CH_2Cl_2)_2$ for the fluorination step (Schemes 5.10 and 5.11). The zinc metal activation step (i.e. use of Rieke zinc) was maintained. Our hypothesis is that if a radical reaction is promoted

by NFSI or oxygen then intramolecular cyclization of the organozinc **5.11** should occur followed by fluorine quench.

Scheme 5.10 Control Experiment

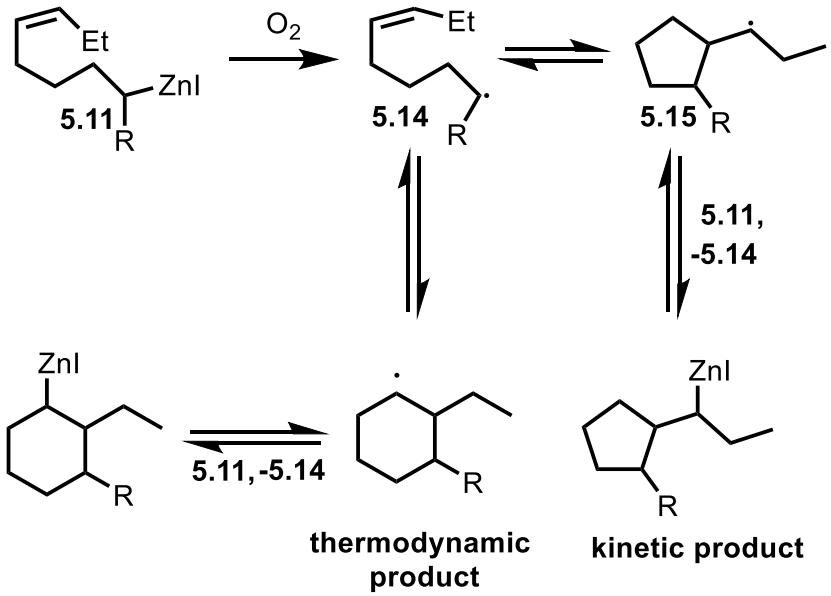


Scheme 5.11 Preliminary Mechanistic Study



The control experiment is illustrated in Scheme 5.10. No cyclized product was isolated which confirms the previously reported results in literature.[19,20] The fluorination experiment was performed as illustrated in Scheme 5.11. To our delight, we observed intramolecular cyclization of organozinc **5.11** to cyclohexanes **5.12** and **5.13** in a 1:1 ratio in 45% yield.

Scheme 5.12 Proposed Radical Chain Propagation for Organozinc 5.11



The regioselectivity of radical cyclization of alkenyl radicals has been extensively investigated.[29-31] Under certain conditions, the 5-membered ring radical intermediate can rearrange into the 6-membered product (Scheme 5.12).[32] In general, the 5-membered cyclized product is considered to be kinetic product, while the 6-membered ring compound is more thermodynamically stable.[33] It is thought that if the original radical is well stabilized, and good hydrogen donors such as THF are absent, then the cyclization will be reversible, making the reaction thermodynamically controlled. This favors the formation of the 6-membered product.[34] To our knowledge, this is the first reported instance of an alkenyl zinc compound undergoing radical cyclization to exclusively form the 6-membered ring in preference to formation of the 5-membered ring product.

5.4 Conclusions

A generalized procedure towards the preparation of monofluorohydrocarbons will have great utility within industry and academia. We report the first instance of electrophilic fluorination of alkyl zinc compounds that proceeds in high yields. The reaction has wide functional group tolerance, and compatibility with 1^o, 2^o, 3^o alkyl and benzylic substrates. We report the first instance of preferential *6-endo-trig* cyclization by organozinc compounds.

5.5 Experimental Section

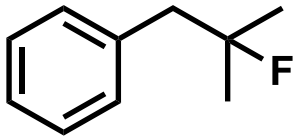
General Considerations

All procedures were carried out under nitrogen atmosphere using standard glove box and Schlenk techniques unless otherwise noted. Column chromatography was performed on 60 Å silica gel (SiliCycle Inc.) using pentane, $C_2H_4Cl_2$, hexanes or mixtures of EtOAc/hexanes as eluents. The ^{1}H, ^{13}C and ^{19}F spectra were recorded on JEOL EC-400 spectrometer using the residual solvent peak as a reference. Compounds for HRMS were analyzed by positive mode electrospray ionization (CI or ESI) using Agilent QTOF mass spectrometer in the Mass Spectrometry Facility (MSF) of the Department of Chemistry and Biochemistry of University of Texas Austin. Reagents and starting materials were obtained from commercial sources and used without further purification unless otherwise noted. Preparation of Rieke zinc and activating zinc (Zn^{*}) by dilute acid followed literature procedure.[7,8]

Synthesis and Characterization

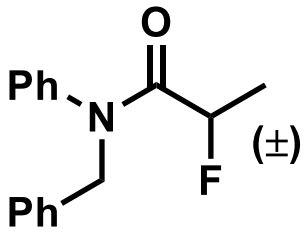
General preparation of Rieke zinc: Compound was synthesized using a modified literature procedure.[8] This procedure and amount was used for all organozinc reagent formation.

In glove box, Li pellets (0.11 g, 16 mmol), and naphthalene (0.2 g, 1.6 mmol) were added to a 25 ml flame dried Schlenk flask equipped with a magnetic stir bar. After removing the flask from the glovebox, the flask was evacuated and refilled with nitrogen three times. THF (10 mL) was added and the mixture stirred until mossy green color persisted. In the glove box a 10 mL flame dried flask equipped with a magnetic stir bar was charged with anhydrous zinc chloride (1.1 g, 8.0 mmol). After removing the flask from the glovebox, it was evacuated and refilled with nitrogen three times followed by addition of THF (15 mL). After, the zinc chloride solution was cannula transferred under positive pressure to the reaction flask. Addition of the zinc salt occurs over 15 min, and after addition the black reaction mixture was stirred for 40 min. The stirring was stopped, and the zinc settled after 40 min. The supernatant was removed via cannula. The Rieke zinc was washed with two consecutive portions of dry THF (15 mL), allowing zinc to settle each time. A final portion of THF (2 mL) was added and the Rieke zinc was ready for use.



2-Fluoro-2-methyl-1-phenylpropane (5.3)

Compound was synthesized using a literature procedure.[43] Purification by column chromatography on silica gel (100% CH_2Cl_2) affording yellow oil (0.60 g, 58%). This compound is known, and its reported spectra matches that reported in literature.[37] ^{1}H NMR ($CDCl_3$, 400 MHz): δ .7.37-7.31 (m, 2H), 7.27-7.19 (m, 3H), 2.85 (d, *J* = 19.2 Hz, 2H), 1.90 (d, *J*=16.4 Hz, 6H).

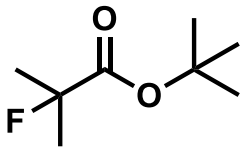


***N*-Benzyl-2-fluoro-*N*-phenylpropionamide 5.4**

General method for organozinc formation: *N*-benzyl-2-bromophenyl propionamide (12.9 mmol, 4.1 g) was placed into a 25 mL flame dried Schlenk flask equipped with a magnetic stir bar. The flask was evacuated and refilled with nitrogen three times. THF (7 mL) was added. The solution was then transferred via syringe to a flame dried 25 mL Schlenk flask equipped with a magnetic stir bar charged with Rieke Zinc. After transferring the halide solution, the mixture was stirred in a 86 ^oC oil bath for 1 hr 30 min, the top of the septum was greased and the stopcock closed to N_2 line. Organozinc compound was titrated with I_2.[43] The reaction was

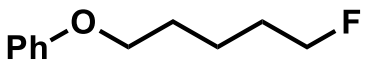
cooled to room temperature, with the stopcock open to nitrogen and the sediments allowed to settle.

General method for fluorination step: The supernatant from the organozinc (0.4 M, 8 mL) was transferred via syringe to a 15 mL flame dried Schlenk flask equipped with a stir bar. Solvent was removed under vacuum for 10 minutes whilst stirring. The flask was back filled with nitrogen, $Cl_2C_2H_4$ (4 mL) was added and solution was cooled to -78 ^oC. NFSI (3.5 mmol, 1.14 g) was quickly added while purging flask with under nitrogen for 3 min. The reaction was warmed to 0 ^oC and stirred for 5 min. The mixture was stirred at room temperature overnight. The reaction was diluted with hexanes (10 mL), mixture was then filtered, then solvent was removed under reduced pressure. Purification by triturating residue 100% hexanes followed by filtration and drying gave white solid (16.4 mg, 90%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.30 (m, 4H), 7.27-7.23 (m, 6H), 4.95 (dd, *J* =14.8 Hz, 2 H), broad signal 2.80 (s, 1H), 0.88 (d, J=5.2 Hz, 3H);$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 176.7 (broad singlet), 142.6, 137.8, 129.4, 128.9 (broad singlet), 128.2 (d, *J*=34.8 Hz), 127.7, 127.1, 53.1, 40.7, 15.5; ^{19}F-NMR (400 MHz, $CDCl_3$) δ -179.1- -179.3 (m, 1F); HRMS (EI) m/z: [M+Na] Calcd for $C_{16}H_{16}FNO$ 280.1108; Found 280.1109.



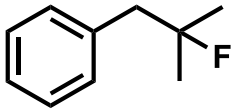
***t*-Butyl-2-fluoro-2-methylpropanoate (5.5)**

The organozinc reagent was prepared from *t*-butyl bromoisobutyrate (3.2 g,14.4 mmol) using the general procedure of **5.4** but in 50 ºC oil bath. The fluorination step was performed as general procedure for **5.4**, using organozinc reagent (0.37 M, 10.0 mL) and NFSI (3.8 mmol, 1.2 g). Purified by column chromatography on silica gel (eluent hexanes:EtOAc 1/0 to 9/1). Calculated yield from ^{19}F-NMR with α,α,α- trifluoro toluene (0.08 mmol, 10 µL) as internal standard, 75% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.47 (d, *J*= 22.4 Hz, 6H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 170.3, 96.2 (d, *J*= 57.7 Hz), 80.1, 25.4, 22.3 (d, *J*= 18.0 Hz);^{19}F-NMR (400 MHz, $CDCl_3$) δ -146.9- -147.0 (m, 1 F). This compound is known.[42]



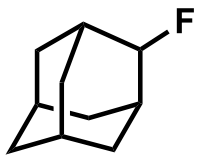
5-Fluoropentoxybenzene (5.6)

The organozinc reagent was prepared from (5-bromopentoxy)benzene (3.2 g, 13.9 mmol) using the general procedure of **5.4**. The fluorination step was performed same as general procedure **5.4**, using organozinc reagent (0.25 M, 16 mL) and NFSI (2.48 mmol, 0.782 g). Purified by column chromatography on silica gel (eluent pentane) affording colorless oil (65.0 mg, 97%) with a slight impurity present. This compound is known, and its reported spectra matches that reported in literature.[39] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (t, *J* =7.6 Hz, 2H), 6.99-6.91 (m, 3H), 4.51 (d, *J* =47.6 Hz, 5.8 Hz, 2H), 4.0 (t, *J*=6.4 Hz), 2.13-2.06 (m, 4 H), 1.99-1.90 (m, 2H).



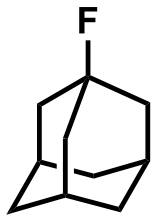
2-Fluoro-2-methyl-1-phenylpropane (5.3)

In glove box, charged a 10 mL flame dried Schlenk flask with Zn^* (0.694 g, 10.7 mmol. After removing the flask from the glove box and placed in 80 ^oC oil bath, THF (8 mL) was added. The mixture was stirred and 2-bromo-2-methyl-1-phenylpropane (8.89 mmol, 1.77 g) was slowly added via syringe. The reaction was stirred for 1hr and 30 min at 80 ^oC. After that, a portion of the organozinc reagent was titrated with I_2.[43] Solid within mixture allowed to settle, then organozinc supernatant (0.1M, 7 mL) was transferred via syringe to a flame dried 10 mL Schlenk flask equipped with a magnetic stir bar. Solvent was removed under high vacuum for 10 min. Dichloroethane (3 mL) was added and solution was cooled to -78 ^oC. Added NFSI (7.0 mmol, 2.2 g) quickly while system purged with nitrogen for 3 min. Reaction was warmed to to 0 ^oC and stirred for 5 min. The mixture was stirred at room temperature overnight. The mixture was purified by prep TLC on silica gel (eluent 100% hexanes) affording product as a colorless oil (72.9 mg, 68%). This compound is known and spectra matches that reported in literature.[37] ^1H NMR ($CDCl_3$, 400 MHz): δ .7.36-7.31 (m, 2H), 7.25-7.20 (m, 3H), 2.87 (d, J = 19.1 Hz, 2H), 1.90 (d, J=16.4 Hz, 6H).



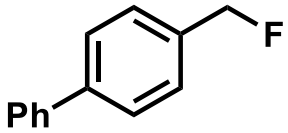
2-Fluoroadamantane (5.7)

The organozinc reagent was prepared from 2-bromo-adamantane (2.0 g, 9.4mmol) using the general procedure of **5.4**. The fluorination step was performed same as general procedure **5.4**, using organozinc reagent (0.4 M, 8.0 mL) and NFSI (3.5 mmol, 1.1 g). Purified by column chromatography on silica gel (eluent CH_2Cl_2) affording white solid (40.9 mg, 83%). This compound is known and its reported spectra matches that reported in literature.[40] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.67 (t, *J*= 24 Hz, 1H), 2.35-2.32 (m, 1H), 2.14-2.06 (m, 3H), 1.96-1.79 (m, 2H), 1.86-1.84 (m, 1H), 1.63-1.53 (m, 3H).



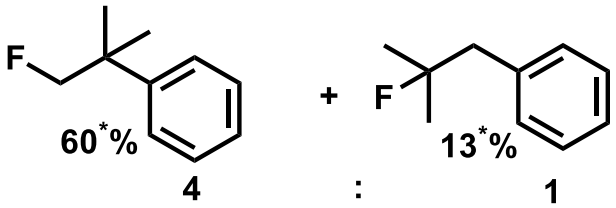
1-Fluoro-adamantane (5.8)

The organozinc reagent was prepared from 1-bromo-adamantane (2.5g, 11.7 mmol) using the general procedure of **5.4**. The fluorination step was performed same as general procedure **5.4**, using organozinc reagent (0.1 M, 5.0 mL) and NFSI (1.0 mmol, 0.32 g). Purified by column chromatography on silica gel (eluent 100% CH_2Cl_2) affording white solid (65.0 mg, 84%). This compound is known and its reported spectra matches that reported in literature.[38] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.71(broad s, 1H), 1.41-1.24 (m, 7H), 0.99-0.86 (m, 7H).



Biphenyl methyl fluoride (5.9)

The organozinc reagent was prepared from *p*-phenylbenzyl bromide (2.0 g, 8.1 mmol) using the general procedure of **5.4**. The fluorination step was performed same as general procedure **5.4**, using organozinc reagent (0.17 M, 11 mL) and NFSI (1.71 mmol, 0.54 g). Purified by column chromatography on silica gel (eluent 100% pentane) affording white solid (29.2 mg, 84%). This compound is known and its reported spectra matches that reported in literature.[35] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (t, *J*=8.0 Hz, 4H), 7.45(t, *J*=8.0 Hz, 4H), 7.36 (t, *J*= 8.0 Hz, 1H), 5.42 (d, *J*=48.0 Hz, 2H).

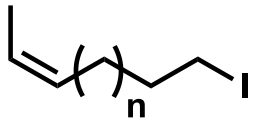


Major: (1-fluro-2-methylpropan-2-yl) benzene (5.2)

Minor: 2-Fluoro-2-methyl-1-phenylpropane (5.3)

The organozinc reagent was prepared from 2-chloro-1,1-dimethyl ethyl benzene (2.0 g, 11.9 mmol) using the general procedure of **5.4** but in 50 ^{o}C oil bath. The fluorination step was performed same as general procedure **5.4**, using organozinc reagent (0.095 M, 12 mL) and NFSI (0.98 mmol, 0.31 g). Purified by column chromatography on silica gel (eluent hexanes:EtOAc 1/0 to 19/1). Calculated yield from ^{19}F-NMR with α,α,α- trifluoro toluene (0.08 mmol, 10 µL) as internal standard, 60%, **5.2** and 13%, **5.3**. The ^{19}F NMR shows two isomers in *ca* 4:1 ratio.

^{1}H NMR spectrum shows two isomers and unreacted 2-chloro-1,1-dimethyl ethyl benzene. ^{1}H NMR ($CDCsl_3$, 400 MHz): δ 7.71-7.41 (m, 15H); product + starting material, 3.87-3.61(m, 4H);products, 3.76(s, 2H); starting material, 1.66-1.58(m, 12H);products, 1.56(s, 6H); starting material; ^{19}F-NMR (400 MHz, CDCl3) δ Major isomer: -218.5 (t, *J* =50.8 Hz,1 F), Minor isomer: -136.5- -136.7 (m, 1F).

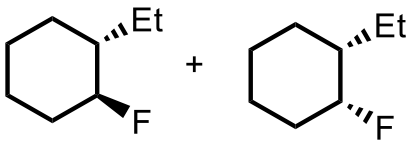


n = 2

***Z*-1-Iodooct-6-ene (5.10)**

After following the general procedure of forming Rieke zinc, the same flask is used for the subsequent organozinc formation step. *Z*-1-Iodooct-6-ene (14.1 mmol, 3.58 g) was placed into the flask. After addition, the mixture was stirred in a 60 ^{o}C oil bath for 30 min, the top of the septum was greased and the stopcock closed. Organozinc compound was titrated with I_2.[43] The reaction was cooled to room temperature, with the stopcock open to nitrogen and the sediments allowed to settle. The supernatant from the organozinc (0.21 M, 6 mL) was transferred via syringe to a 15 mL flame dried Schlenk flask equipped with a stir bar. Solvent was removed under vacuum for 10 mins while stirring. The flask was back filled with nitrogen, $Cl_2C_2H_4$ (6 mL) and solution was cooled to -78 ^{o}C. Iodine (12.6 mmol, 3.2 g) was quickly added while purging system with nitrogen for 3 min. The reaction was warmed to 0 ^{o}C, and stirred for 5 min. The mixture was stirred at room temperature overnight. The reaction with hexanes (20 mL), mixture was then filtered, then solvent was removed under reduced pressure. Purified by

using column chromatography on silica gel (eluent 100% hexanes) affording colorless oil (26.5 mg, 94%). This compound is known and its reported spectra matches that reported in literature.[36] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.32 (dt, *J*= 8.0 Hz, 8.0 Hz, 2H), 3.16 (t, *J*=4.0 Hz, 2H), 2.03-1.97 (m, 4H), 1.81-1.78 (m, 2H), 1.44-1.40 (m, 2H), 0.94 (t, *J*= 8.0Hz, 3H).



***Cis*- and *trans*- 1-ethyl-2-fluorocyclohexane (5.12 and 5.13)**

The organozinc reagent was prepared from *Z*-1-idooct-6-ene (3.6 g, 15.1mmol) using the general procedure of **5.4**. The fluorination step was performed same as general procedure **5.4**, using organozinc reagent (0.22 M, 6.0 mL) and NFSI (13.3 mmol, 4.2 g). Purified by column chromatography on silica gel (eluent 100% pentane). Calculated yield from ^{19}F-NMR with α,α,α- trifluoro toluene (0.08 mmol, 10 µL) as internal standard, 45%. The ^{19}F NMR shows two isomers in *ca* 1:1 ratio. ^{1}H NMR spectrum shows two isomers and pentane.^{1}H NMR ($CDCl_3$, 400 MHz): δ products signal 4.32-4.2 (m, 1H), 3.76-3.62 (m, 1H), 1.64-1.59 (m, 1H), 1.56 (s, 1H), 1.51-1.45 (m, 1H), 1.41 (m, 1H), 1.11-0.99 (m, 1H), 0.96-0.94 (m, 1H); pentane + product signal: 1.36-1.21 (m, 14H), 0.89-0.82 (m, 12 H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): C-F couplings not resolved, list of signals provided due to complexity of spectrum δ 68.4, 66.1, 41.1, 35.8, 35.3, 32.8,30.6, 29.7, 27.8, 14.6, 11.6, 6.23; ^{19}F-NMR (400 MHz, CDCl3) δ -175.2 - -175.8 (m, 1 F), -176.4- -176.9 (m, 1F).These compound are known.[41]

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