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The Reactivity of Potassium Carbanions with Epoxides

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THE REACTIVITY OF POTASSIUM CARBANIONS WITH EPOXIDES

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Dedication

This dissertation is dedicated to my parents Maria Cristina and Raul Ruben Alvarado
to my brother and sister, Ruben and Erika,
to my grandmother Emma Morales
and to my husband Arturo Dorado.

THE REACTIVITY OF POTASSIUM CARBANIONS WITH EPOXIDES

by

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Abstract

The reaction of α -cumylpotassium and cyclohexene oxide produces *trans*-cumylcyclohexanol in high yield in the presence of excess cumene. Reactions of 1.1 and 2.0 equivalents of cumene with one equivalent of *n*-butylpotassium to make α -cumylpotassium were shown to take several days to reach a maximum yield in the subsequent reaction of α -cumylpotassium and cyclohexene oxide. Although it was initially hypothesized that the high yield was attributed to the interaction of the potassium with the aromatic rings of the α -cumyl anion and the excess cumene, which was confirmed by molecular modeling studies, these reactions demonstrated that no large excess of aromatic solvents were needed. Substituting benzene and *tert*-butylbenzene for cumene in this reaction gave lower yields of product.

Cyclohexene oxide reacted with *n*-butylpotassium to unexpectedly produce 2-butylcyclohexanone in a 2 % isolated yield or in a 10 % isolated yield of its semi-carbazone derivative. Based on the literature, we hypothesized that we produced 2-butylcyclohexanone by first opening the epoxide ring of cyclohexene oxide by S_N2 substitution with *n*-butylpotassium to give the alkoxide of *trans*-2-butylcyclohexan-1-ol as observed in the reaction of cyclohexene oxide and α -cumylpotassium. Next, a second equivalent of *n*-butylpotassium reacted with cyclohexene oxide to produce a carbene alkoxide. Finally, the carbene alkoxide oxidized the alkoxide of *trans*-2-butylcyclohexan-1-ol to 2-butylcyclohexanone. This mechanism implies that a greater than 33 % yield is not possible.

The reaction of 2-methyl-1,2-epoxycyclohexane with *n*-butylpotassium and the reaction of cyclohexene oxide with *sec*-butyllithium did not lead to any ring opening products.

Table of Contents

Acknowledgements.....	v
Abstract.....	vi
Table of Contents.....	vii
List of Tables	x
List of Figures.....	xi
List of Equations.....	xiii
List of Schemes.....	xiv
Chapter 1: Introduction.....	1
Chapter 2: Results and Discussion.....	8
2.1 Molecular Modeling Studies of α -Cumylpotassium, Lithium, and Sodium.....	8
2.2 Solvent Effect of Cumene Substitution with Benzene and <i>tert</i> -Butylbenzene.....	10
2.2.1 Substitution of Cumene with Benzene.....	10
2.2.2 Substitution of Cumene with <i>tert</i> -Butylbenzene.....	12
2.3 Kinetic Studies on the Reaction of α -Cumylpotassium with Cyclohexene Oxide.....	13
2.3.1 Production of <i>trans</i> -Cumylcyclohexanol in the Presence of 1.1 Equivalents of Cumene.....	13
2.3.2 Production of <i>trans</i> -Cumylcyclohexanol in the Presence of 2.0 Equivalents of Cumene.....	15
2.4 Reactivity of Other Organopotassium Species.....	17
2.4.1 Reaction of <i>n</i> -Butylpotassium and Cyclohexene Oxide.....	17
2.4.2 Reaction of <i>n</i> -Butyllithium and Cyclohexene Oxide.....	20
2.4.3 Isolation and Analysis of 2-Butylcyclohexanone.....	21
2.4.4 Derivatization of 2-Butylcyclohexanone.....	23
2.4.5 Hypotetical Mechanism for Formation of 2-Butylcyclohexanone.....	25

2.4.6	Reaction of <i>sec</i> -Butylpotassium and Cyclohexene Oxide.....	30
3.0	Conclusions.....	32
4.0	Experimental.....	36
4.1	Materials.....	36
4.2	Equipment.....	36
4.2.1	Rotary Evaporator.....	36
4.2.2	Horizontal Distillation.....	36
4.2.3	Chiral Column High Performance Liquid Chromatography.....	36
4.2.4	Radial Chromatography and UV Light.....	37
4.2.5	Melting-Point Apparatus.....	37
4.2.6	Nuclear Magnetic Resonance (NMR).....	37
4.2.7	Mass Spectrometer.....	37
4.3	Experimental.....	38
4.3.1	Attempted Synthesis of <i>trans</i> -Cumylcyclohexanol in the Presence of Benzene.....	38
4.3.2	Attempted Synthesis of <i>trans</i> -Cumylcyclohexanol in the Presence of <i>tert</i> -Butylbenzene.....	39
4.3.3	Synthesis of <i>trans</i> -Cumylcyclohexanol with 1.1 Equivalents of Cumene.....	39
4.3.4	Synthesis of <i>trans</i> -Cumylcyclohexanol with 2.0 Equivalents of Cumene.....	40
4.3.5	Synthesis of 2-Butylcyclohexanone.....	42
4.3.6	Synthesis of 2-Butylcyclohexanone Semicarbazone.....	43
4.3.7	Attempted Synthesis of Cyclohexanone.....	43
4.3.8	Attempted Synthesis of 2-Butyl-1-Methylcyclohexan-1-ol.....	44
4.3.9	Reaction of <i>sec</i> -Butylpotassium and Cyclohexene Oxide.....	44

References	46
Curriculum Vitae	49

List of Tables

Table 2.1: 1.1 Equivalents of Cumene, Kinetic Experiment Conditions and Results	14
Table 2.2: 2.0 Equivalents of Cumene, Kinetic Experiment Conditions and Results.	16

List of Figures

Figure 1.1: Super-Base or LiCKOR Reagent.....	3
Figure 1.2: Interaction of Potassium with Aromatic Rings of Cumene.....	6
Figure 1.3: Production of Potassium Triazenide.....	6
Figure 1.4: Structure of Potassium Dihydroborate and Toluene.....	6
Figure 1.5: [K(2-Benzylphenol) ₃][2-Benzylphenolate] Structure.....	7
Figure 1.6: Synthesis and Structure of Potassium Bridged Borole Compound.....	7
Figure 2.1: Optimization Calculations of α -Cumylpotassium and Cumene.....	8
Figure 2.2: Optimization Calculations of α -Cumyllithium and Cumene.....	9
Figure 2.3: Optimization Calculations of α -Cumylsodium and Cumene.....	9
Figure 2.4: Chiral HPLC Chromatogram and Data for TCC Synthesis in the Presence of Benzene.....	11
Figure 2.5: Chiral HPLC Chromatogram and Data for a TCC Standard Solution.....	11
Figure 2.6: Chiral HPLC Chromatogram and Data for TCC Synthesis in the Presence of <i>tert</i> -Butylbenzene.....	12
Figure 2.7: Time vs. Percent Yield of the 1.1 and 2.0 Equivalents of Cumene Reactions.....	16
Figure 2.8: ¹³ C NMR Spectrum of Crude Product from the Reaction of <i>n</i> -Butylpotassium and Cyclohexene Oxide.....	18
Figure 2.9: ¹ H NMR Spectrum of Crude Product from the Reaction of <i>n</i> -Butylpotassium and Cyclohexene Oxide.....	19
Figure 2.10: DEPT-135 Spectrum of Crude Product from the Reaction of <i>n</i> -Butylpotassium and Cyclohexene Oxide.....	19
Figure 2.11: ¹³ C NMR Spectrum of Crude Product from the Reaction of <i>n</i> -Butyllithium and Cyclohexene Oxide.....	20
Figure 2.12: ¹³ C NMR Spectrum of First Fraction Isolated by Radial Chromatography.....	21
Figure 2.13: Mass Spectrum with Parent Peak for 2-Butylcyclohexanone.....	22

Figure 2.14: ^{13}C NMR of 2-Butylcyclohexanone Semicarbazone.....	24
Figure 2.15: Calculated ^{13}C NMR for 2-Butylcyclohexanone Semicarbazone.....	24
Figure 2.16: X-Ray Fluorescence of Potassium <i>tert</i> -Amylate.....	25
Figure 2.17: ^{13}C NMR of Crude Product from the Reaction of <i>n</i> -Butylpotassium and Cyclohexene Oxide in the Presence of Cyclohexanol.....	28
Figure 2.18: ^{13}C NMR of Crude Product from the Reaction of <i>n</i> -Butylpotassium with 1-Methyl- 1,2-Epoxycyclohexane.....	30
Figure 2.19: ^{13}C NMR of Crude Product from the Reaction of <i>sec</i> -Butylpotassium and Cyclohexene Oxide.....	31

List of Equations

Equation 2.1: Calculation of Percent Yield for TCC Synthesized in the Presence of Benzene.....	12
Equation 2.2: Calculation of Percent Yield for TCC Synthesized in the Presence of <i>tert</i> -Butylbenzene.....	13

List of Schemes

Scheme 1.1: Reaction of Mono-Substituted Epoxides with Alkyl Lithium or Grignard Reagent to Produce the Corresponding Alcohol.....	1
Scheme 1.2: Reaction of <i>n</i> -Butyllithium and Cyclohexene Oxide to Produce the Elimination Product.....	1
Scheme 1.3: Reaction of <i>n</i> -Butyllithium and Cyclohexene Oxide in the Presence of BF ₃ •Et ₂ O to Produce the Substitution Product.....	2
Scheme 1.4: Reaction of <i>n</i> -Propyl Magnesium Bromide with Cyclohexene Oxide to Produce Ring Opening Products.....	2
Scheme 1.5: Reaction of <i>trans</i> -2,3-Dimethyloxirane, <i>tert</i> -Butyl Magnesium Chloride, and Copper Cyanide to Produce a Ring Opening Product.....	2
Scheme 1.6: Reaction of Cyclohexene Oxide and Phenyl Magnesium Chloride in the Presence and Absence of Copper Iodide to Produce <i>trans</i> -2-Phenylcyclohexan-1-ol.....	3
Scheme 1.7: Production of Trimethylsilyl Derivative of Tetrahydropyran.....	3
Scheme 1.8: Ring Opening Reaction of α -Cumylpotassium and Cyclohexene Oxide to Produce <i>trans</i> -Cumylcyclohexanol (TCC).....	4
Scheme 1.9: Potassium-Lithium Ion Exchange Reaction of <i>n</i> -Butyllithium and Potassium <i>tert</i> -Amylate.....	5
Scheme 1.10: Synthesis of α -Cumylpotassium from Cumene and <i>n</i> -Butylpotassium.....	5
Scheme 1.11: Reaction of Three Equivalents of Cumene and <i>n</i> -Butylpotassium Followed by Cyclohexene Oxide to Produce TCC in High Yield.....	5
Scheme 2.1: Substitution of Cumene with Other Aromatic Solvents in the Synthesis of TCC....	10
Scheme 2.2: Substitution of Cumene with Benzene in the Synthesis of TCC.....	10
Scheme 2.3: Substitution of Cumene with <i>tert</i> -Butylbenzene in the Synthesis of TCC.....	12
Scheme 2.4: Reaction Scheme for Kinetic Experiments.....	14
Scheme 2.5: Equilibrium of <i>meta</i> and <i>para</i> Metalated Cumene and the Thermodynamically Favored α -Cumylpotassium.....	15
Scheme 2.6: Reaction of <i>n</i> -Butylpotassium and Cyclohexene Oxide.....	17

Scheme 2.7: Reaction of <i>n</i> -Butylpotassium and Cyclohexene Oxide to Produce 2-Butylcyclohexanone.....	22
Scheme 2.8: Reaction of 2-Butylcyclohexanone with Semicarbazide to Produce 2-Butylcyclohexanone Semicarbazone.....	23
Scheme 2.9: Rearrangement of Epoxides to Enolates Through a Carbene Intermediate.....	26
Scheme 2.10: Reaction of a Secondary Metal Alkoxide with a Carbene to Produce a Ketone.....	26
Scheme 2.11: Hypothesized Mechanism for the Production of 2-Butylcyclohexanone.....	27
Scheme 2.12: Reaction of <i>n</i> -Butylpotassium with Cyclohexene Oxide in the Presence of Cyclohexanol to Produce Cyclohexanone.....	27
Scheme 2.13: Reaction of 1-Methyl-1,2-Epoxy cyclohexane with <i>n</i> -Butylpotassium to Produce 2-Butyl-1-Methylcyclohexan-1-ol.....	29
Scheme 2.14: Suspected Rearrangement of 1-Methyl-1,2-Epoxy cyclohexane to the Corresponding Ketone.....	29
Scheme 2.15: Production of <i>sec</i> -Butylpotassium.....	30
Scheme 3.1: Reaction of an Intermediate Dianion with a Carbene to Produce Cyclohexenol.....	35

Chapter 1: Introduction

The creation of carbon-carbon bonds is an essential part of organic synthesis for the production of new molecules. Carbon-carbon bonds can be formed in nucleophilic reactions such as the nucleophilic substitution reaction of a carbon nucleophile with epoxides to produce 1,2-difunctionalized molecules such as 1,2-amino alcohols, 1,2-diols, 1,2-mercapto alcohols and 1,2-halohydrins¹. These 1,2-difunctionalized molecules are utilized to produce natural products such as (±)-Puctaporonin C, a tetracyclic sesquiterpene² as well as hydroxy-Freidinger lactams which are used to produce biologically active peptidomimetics³.

The nucleophilic ring opening reaction of unsymmetric epoxides containing a primary carbon is regioselective and leads to substitution at the less substituted and less sterically hindered position in high yields^{4,5} (Scheme 1.1).

Scheme 1.1 Reaction of Mono-Substituted Epoxides with Alkyl Lithium or Grignard Reagents to Produce the Corresponding Alcohol⁵.

In contrast, when *n*-butyllithium reacts with cyclohexene oxide, an epoxide with secondary carbons, the elimination product is obtained exclusively (Scheme 1.2)⁶.

Scheme 1.2 Reaction of *n*-Butyllithium and Cyclohexene Oxide to Produce the Elimination Product⁶.

In order to obtain the substitution product, organolithium reagents must be reacted with epoxides in the presence of a Lewis acid. When *n*-butyllithium and cyclohexene oxide are reacted in the presence of boron trifluoride etherate, 2-butylcyclohexanol can be obtained in a yield of 97% (Scheme 1.3)⁷.

Scheme 1.3 Reaction of *n*-Butyllithium and Cyclohexene Oxide in the Presence of BF₃•Et₂O to Produce the Substitution Product⁷.

Grignard reagents must be converted to an organo-cuprate before reacting with secondary epoxides to give ring opening products (Schemes 1.4, 1.5, and 1.6)⁸⁻¹⁰. This is due to the fact that copper is less electropositive than lithium and magnesium, making the bond between copper and the alkyl group less polar⁴.

Scheme 1.4 Reaction of *n*-Propyl Magnesium Bromide with Cyclohexene Oxide to Produce Ring Opening Products⁸.

Scheme 1.5 Reaction of *trans*-2,3-Dimethyloxirane, *tert*-Butyl Magnesium Chloride, and Copper Cyanide to Produce a Ring Opening Product⁹.

Scheme 1.6 Reaction of Cyclohexene Oxide and Phenyl Magnesium Chloride in the Presence and Absence of Copper Iodide to Produce *trans*-2-Phenylcyclohexan-1-ol¹⁰.

Literature describes the combination of a potassium alkoxide and butyl lithium as a “super-base” or LiCKOR-reagent with metalating capabilities (Figure 1.1)¹¹.

Figure 1.1 Super-Base or LiCKOR Reagent¹¹.

When this reagent has been introduced to various hydrocarbons they undergo a hydrogen/metal exchange reaction or deprotonation¹¹. Alkyl potassiums^{12,14,15} prepared in a similar manner¹¹ have also been reacted with ferrocene¹², α -olefins¹³, toluene, cross-linked polystyrene derivatives¹⁴ and saturated ethers to produce the metalated products¹²⁻¹⁵. For example, in Scheme 1.7 tetrahydropyran is first reacted with *n*-butylpotassium to give the metalated product followed by reaction with chlorotrimethylsilane to give the trimethylsilyl derivative¹⁵.

Scheme 1.7 Production of Trimethylsilyl Derivative of Tetrahydropyran¹⁵.

Based on this knowledge it may be expected that *n*-butylpotassium prepared this way¹¹ would simply metalate an epoxide but this is not the case. In particular Comins and Salvador

found that secondary epoxides react with α -cumylpotassium to produce *trans*-cumylcyclohexanol (TCC)¹⁶ (Scheme 1.8).

Scheme 1.8 Ring Opening Reaction of α -Cumylpotassium and Cyclohexene Oxide to Produce *trans*-Cumylcyclohexanol (TCC)¹⁶.

Based on the reactivity of organolithium and magnesium reagents with cyclohexene oxide it would be expected that α -cumylpotassium would not react with cyclohexene oxide in a nucleophilic substitution fashion but perhaps would perform elimination. It is therefore unusual that this tertiary organopotassium species can react with cyclohexene oxide in a substitution fashion without the need for activators such as boron trifluoride as is necessary for organolithiums or for conversion to organocuprates which are necessary for organomagnesium reagents.

In reality the reaction of α -cumylpotassium and cyclohexene oxide to produce TCC (Scheme 1.8) consists of three reactions all done in one pot. First a potassium-lithium ion exchange reaction is completed to form *n*-butylpotassium (Scheme 1.9), followed by the reaction of *n*-butylpotassium and cumene to make α -cumylpotassium (Scheme 1.10), after two days cyclohexene oxide is added, and after two hours the reaction is quenched with water and the desired, TCC, is obtained (Scheme 1.11).

The preparation of *n*-butylpotassium by a potassium-lithium ion exchange reaction avoids using highly reactive and unstable potassium metal (Scheme 1.9).

Scheme 1.9 Potassium-Lithium Ion Exchange Reaction of *n*-Butyllithium and Potassium *tert*-Amylate.

Because *n*-butylpotassium is such a strong base it can deprotonate cumene at its benzylic position and on the phenyl ring (Scheme 1.10). It therefore takes two days to allow the equilibrium to favor deprotonation of the cumene at the benzylic position to make the α -cumyl anion¹⁷.

Scheme 1.10 Synthesis of α -Cumylpotassium from Cumene and *n*-Butylpotassium¹⁷.

As shown in Scheme 1.11 in the reaction the yield increases proportionately with the amount of cumene used to 93%¹⁶ with three equivalents.

Scheme 1.11 Reaction of Three Equivalents of Cumene and *n*-Butylpotassium Followed by Cyclohexene Oxide to Produce TCC in High Yield¹⁶.

The initial hypothesis of why three equivalents of cumene are required for this reaction was that the *d*-orbitals of potassium were interacting with the aromatic portion of the solvent as presented in Figure 1.2.

Figure 1.2 Interaction of Potassium with Aromatic Rings of Cumene.

There are various examples of the interaction of potassium with aromatic groups in the literature¹⁸⁻²¹. For example, after metalation of the triazene ($\text{C}_6\text{H}_3\text{-2,6-(C}_6\text{H}_2\text{-2,4,6-}^i\text{Pr}_3)_2\text{N}_3\text{H}$), interaction of potassium with the flanking arene rings of diaryltriazenido ligands is observed in the resulting alkali-metal salt (Figure 1.3)¹⁸.

Figure 1.3 Production of Potassium Triazenide¹⁸.

Potassium is observed to interact with toluene, a solvent utilized in the formation of the potassium dihydroborate in Figure 1.4¹⁹.

Figure 1.4 Structure of Potassium Dihydroborate and Toluene¹⁹.

Separation of the potassium ion was successful after potassium carbonate was reacted with 2-benzylphenol²⁰. The resulting structure $[\text{K(2-Benzylphenol)}_3][\text{2-Benzylphenolate}]$

illustrates the interaction of potassium with the phenolic oxygen atom and benzyl ring²⁰ (Figure 1.5).

Figure 1.5 [K(2-Benzylphenol)₃][2-Benzylphenolate] Structure²⁰.

The adduct of 1,3-dimesitylimidazolidin-2-ylidene and 1-chloro-2,3,4,5-tetraphenylborole was reduced by KC₈/Et₂O to give, after crystallization, the potassium bridged dimer illustrated in Figure 1.6²¹.

Figure 1.6 Synthesis and Structure of Potassium Bridged Borole Compound²¹.

The goal of this research was to study the reaction of potassium carbanions, such as α -cumylpotassium, with epoxides. We began by studying the interaction of potassium with the aromatic rings of cumene and the α -cumyl anion (Figure 1.2) through molecular modeling. In order to verify that the interaction of potassium with the aromatic rings of cumene and the α -cumyl anion are indeed the reason behind the increased yield observed in Scheme 1.11, cumene was substituted with other aromatic solvents. Finally, non-benzilic organopotassium reagents were reacted with epoxides in order to observe their reactivity and compare their reactivity to that of α -cumylpotassium and cyclohexene oxide (Scheme 1.11).

Chapter 2: Results and Discussion

2.1 Molecular Modeling Studies of α -Cumylpotassium, Lithium, and Sodium

The structure of α -cumylpotassium and two equivalents of cumene was optimized using the AMPAC 9.1 software package from Semichem Inc. (Figure 2.1). The PM6 model method was required to handle the presence of potassium.

Figure 2.1 Optimization Calculations of α -Cumylpotassium and Cumene.

According to the optimized AMPAC model, potassium is centered over the cumyl anion aromatic ring for maximum overlap between carbon Pi orbitals and the potassium *d*-orbitals. This leaves the benzylic position of our α -cumyl anion open and flat making it less sterically hindered and a more effective nucleophile. The optimized model also shows coordination of potassium to the aromatic rings of cumene.

Optimization calculations were completed on the structures of α -cumyllithium and two equivalents of cumene utilizing AMPAC 9.1 and the parameters described previously. The lithium ion was closer to the benzylic position of the α -cumyl anion and seemed to be interacting with the benzylic position and partially with the aromatic ring of one of the cumene equivalents (Figure 2.2).

Figure 2.2 Optimization Calculations of α -Cumyllithium and Cumene.

The structure of α -cumylsodium and two equivalents of cumene was also optimized utilizing AMPAC 9.1 and the same parameters utilized for the potassium and lithium calculations. The interaction between the sodium ion and the benzylic position of the α -cumyl anion is stronger than that of the lithium calculations. There also seems to be an interaction between the hydrogens of the methyl of the cumyl anion with the sodium cation (Figure 2.3).

Figure 2.3 Optimization Calculations of α -Cumylsodium and Cumene.

The molecular models confirm that α -cumylpotassium varies from the other examples because of the d -orbital interactions that are only available to potassium but not to lithium or sodium. This is also confirmed from the difficulty in isolating an α -cumyl species with lithium²² or sodium²³.

2.2 Solvent Effect of Cumene Substitution with Benzene and *tert*-Butylbenzene

Observing that the molecular models show an interaction between potassium and the aromatic solvent, we studied the solvent effect on the reaction of α -cumylpotassium with cyclohexene oxide. To do this α -cumylpotassium was prepared with only one equivalent of cumene and two or more equivalents of different aromatic solvents (Scheme 2.1). The alternative aromatic solvents used were benzene and *tert*-butylbenzene as outlined below. The yields of the reaction of three equivalents of cumene to using one equivalent of cumene and two or more equivalents of other aromatic solvents were compared.

Scheme 2.1 Substitution of Cumene with Other Aromatic Solvents in the Synthesis of TCC.

2.2.1 Substitution of Cumene with Benzene

The first aromatic solvent that was tested was benzene. In this reaction two equivalents of cumene were substituted with three equivalents of benzene (Scheme 2.2) when forming α -cumylpotassium, and after two days cyclohexene oxide was added and the reaction was quenched with water. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over potassium carbonate, filtered, and reduced to give the crude reaction mixture of 1.28 g. A portion of this mixture (0.600 g) was dissolved in hexanes to give a 5 mL solution for further analysis.

Scheme 2.2 Substitution of Cumene with Benzene in the Synthesis of TCC.

The amount of TCC present in the crude reaction mixture was determined by Chiral column High Performance Liquid Chromatography (HPLC). An ultraviolet-visible (UV) detector wavelength of 215 nm was utilized to ensure that the TCC enantiomer peaks were equal. Otherwise overlap with other compounds was observed at the standard 256 nm. The area under the first enantiomer peak of a 3 μ L sample was compared to the area under the first enantiomer peak of a 1 μ L sample of a TCC solution of known concentration (0.122 g/10 mL hexanes solution). The chromatograms and area data of both solutions are shown in Figures 2.4 and 2.5.

Peak #	AREA %	RT	AREA
1	49.461	8.47	31457058
2	50.539	9.69	32142146

Figure 2.4 Chiral HPLC Chromatogram and Data for TCC Synthesis in the Presence of Benzene.

Peak #	AREA %	RT	AREA
1	50.227	8.64	20794129
2	49.773	9.86	20605964

Figure 2.5 Chiral HPLC Chromatogram and Data for a TCC Standard Solution.

Once the HPLC results for TCC synthesized with benzene solvent and the standard were obtained, dimensional analysis was utilized to determine that the yield was 3% given that the theoretical yield was 2.15 g (Equation 2.1).

$$\frac{0.122\text{g}}{10\text{ mL}} \times \frac{1\text{mL}}{10^3\mu\text{L}} \times \frac{1\mu\text{L}}{1} \times \frac{31457058}{20794129} \times \frac{5\text{mL}}{0.600\text{g}} \times \frac{10^3\mu\text{L}}{1\text{mL}} \times \frac{1}{3\mu\text{L}} \times \frac{1.28\text{g}}{2.15\text{g}} \times 100\% = 3\%$$

Equation 2.1 Calculation of Percent Yield for TCC Synthesized in the Presence of Benzene.

2.2.2 Substitution of Cumene with *tert*-Butylbenzene

For the reaction with benzene it was noted that a precipitate formed versus the homogenous suspension observed in the reaction when three equivalents of cumene were used. Believing that the difference in the yield of the reactions was due to solubility, *tert*-butylbenzene was tested. Two equivalents of *tert*-butylbenzene were used in the same reaction sequence as previously described for benzene (Scheme 2.3). HPLC analysis was performed on 3 μL of a crude reaction sample solution of 0.134 g in 10 mL of hexanes (Figure 2.6) and the percent yield was determined to be 27 % (Equation 2.2).

Scheme 2.3 Substitution of Cumene with *tert*-Butylbenzene in the Synthesis of TCC.

Peak#	AREA%	RT	AREA
1	50.083	9.06	38571826
2	49.917	10.36	38444028

Figure 2.6 Chiral HPLC Chromatogram and Data for TCC Synthesis in the Presence of *tert*-Butylbenzene.

$$\frac{0.122\text{g}}{10\text{ mL}} \times \frac{1\text{mL}}{10^3\mu\text{L}} \times \frac{1\mu\text{L}}{1} \times \frac{38571826}{20794129} \times \frac{10\text{mL}}{0.134\text{g}} \times \frac{10^3\mu\text{L}}{1\text{mL}} \times \frac{1}{3\mu\text{L}} \times \frac{1.024\text{g}}{2.15\text{g}} \times 100 = 27\%$$

Equation 2.2 Calculation of Percent Yield for TCC Synthesized in the Presence of *tert*-Butylbenzene.

2.3 Kinetic Studies on the Reaction of α -Cumylpotassium with Cyclohexene Oxide

The increased yield was consistent with the observation that the *tert*-butylbenzene reaction was more homogeneous than the benzene reaction, but the yields for both reactions were much lower than that of the original reaction. At this point we began to question the validity of our original hypothesis that predicted the formation of a complex with the α -cumyl anion and the aromatic solvent (Figure 1.2). We realized that if we needed three equivalents of cumene to form the hypothesized complex: One to form the α -cumyl anion and two others to interact with the potassium ion then a reaction in which one equivalent of cumene was utilized could never produce more than a 30% yield. Regardless of how long the reaction was allowed to run, an experiment in which two equivalents of cumene were utilized would never exceed a 60% yield. On the contrary, if the yield exceeded 30% for a one equivalent reaction and 60% for a two equivalent experiment over a period of time then we would prove that the reaction yield is an issue of kinetics and not the amount of aromatic solvent present.

2.3.1 Production of *trans*-Cumylcyclohexanol in the Presence of 1.1 Equivalents of Cumene

We predicted that the increase in yield was due to the rate of the reaction of *n*-butylpotassium and cumene to produce α -cumylpotassium (Scheme 1.10). Our goal was to determine if the overall yield of the reaction would increase over time if the amount of cumene

was kept constant. In order to accomplish this goal, a series of reactions were set up simultaneously in which the amount of cumene utilized was 1.1 equivalents and all the other reagents were kept constant. The only difference was the amount of time allowed prior to adding cyclohexene oxide to the reaction (Scheme 2.4 and Table 2.1).

Scheme 2.4 Reaction Scheme for Kinetic Experiments.

Table 2.1 1.1 Equivalents of Cumene, Kinetic Experiment Conditions and Results.

Flask	Potassium <i>tert</i> -Amylate	Cumene	<i>n</i> -Butyllithium	Time (Days)	Cyclohexene Oxide	Yield (%)
1	1.2 eq	1.1 eq	1eq	2	1 eq	49
2	1.2 eq	1.1 eq	1eq	4	1eq	67
3	1.2 eq	1.1 eq	1eq	6	1eq	68
4	1.2 eq	1.1 eq	1eq	8	1eq	74
5	1.2 eq	1.1 eq	1eq	10	1eq	67

The reason behind utilizing 1.1 equivalents of cumene and not 1 equivalent of cumene lies in previous work done by Benkeeser. As mentioned previously, the reaction of *n*-butylpotassium with cumene to produce α -cumylpotassium takes two days (Scheme 1.10)¹⁷. This is because deprotonation occurs first on the aromatic ring of cumene, particularly at the *meta* and *para* positions and it is only after two days that the thermodynamically favored product, which

requires deprotonation at the benzylic position, can be obtained in the presence of excess cumene (Scheme 2.5)¹⁷. In other words, without excess cumene no equilibration between ring and benzylic anions is possible.

Scheme 2.5 Equilibrium of *meta* and *para* Metalated Cumene and the Thermodynamically Favored α -Cumylpotassium⁹.

2.3.2 Production of *trans*-Cumylcyclohexanol in the Presence of 2.0 Equivalents of Cumene

After two days the yield of the 1.1 equivalent reaction was 49% and after eight days a yield of 74% was achieved. It was then determined that a second set of reactions should be carried out in which 2 equivalents of cumene were utilized (Table 2.2).

The yield for the two equivalent reaction was determined after one day because it was unclear as to how much of an effect the extra cumene would have on the rate of the reaction. The yield after one day was 65% and after eight days the yield reached a high of 72%. A plot of the yields for both the 1.1 and 2 equivalent experiments is shown in Figure 2.7.

Table 2.2 2.0 Equivalents of Cumene, Kinetic Experiment Conditions and Results.

Flask	Potassium <i>tert</i> -Amylate	Cumene	<i>n</i> -Butyllithium	Time (Days)	Cyclohexene Oxide	Yield (%)
1	1.2 eq	2 eq	1eq	1	1eq	65
2	1.2 eq	2 eq	1eq	2	1eq	71
3	1.2 eq	2 eq	1eq	4	1eq	71
4	1.2 eq	2 eq	1eq	6	1eq	69
5	1.2 eq	2 eq	1eq	8	1eq	72
6	1.2 eq	2 eq	1eq	10	1eq	58

Figure 2.7 Time vs. Percent Yield of the 1.1 and 2.0 Equivalents of Cumene Reactions.

It was noted that for both the 1.1 and 2 equivalent reactions there was a significant decrease in yield after day eight. This was attributed to evaporation of cumene and its absorption

into the septum as well as the inability to exclude air and water from the anhydrous environment for extended periods of time. It is also possible that the decrease was due to other reactions that can occur over prolonged periods of time as observed for α -cumyl lithium²² and sodium²³ reagents.

2.4 Reactivity of Other Organopotassium Species

After studying the α -cumylpotassium reaction extensively, our attention was turned to other examples of organopotassium species that are not benzilic because it was demonstrated that an aromatic solvent is not necessary to carry out the ring opening reactions of potassium anions with epoxides.

2.4.1 Reaction of *n*-Butylpotassium and Cyclohexene Oxide

We decided to investigate the reaction of *n*-butylpotassium with cyclohexene oxide (Scheme 2.6) and compare its reactivity to that of the tertiary benzilic organopotassium species, α -cumylpotassium. We chose to study *n*-butylpotassium because it is a primary organopotassium species that was readily available to us through the potassium-lithium ion exchange reaction of potassium *tert*-amylate and *n*-butyllithium (Scheme 1.9).

Scheme 2.6 Reaction of *n*-Butylpotassium and Cyclohexene Oxide.

α -Cumylpotassium, a tertiary organopotassium species, attacks cyclohexene oxide at its secondary position through a substitution mechanism to produce *trans*-cumylcyclohexanol. It was predicted that in the case of the primary organopotassium species, *n*-butylpotassium, that

substitution would also lead to the production of *trans*-2-butylcyclohexan-1-ol (Scheme 2.6). Carbon 13 Nuclear Magnetic Resonance (^{13}C NMR) of the product mixture did not give any indication of the production of an alcohol but there was indication of the presence of a carbonyl group at a chemical shift of 213.7 ppm (Figure 2.8). Proton NMR (^1H NMR) and Distortionless Enhancement by Polarization Transfer-135° (DEPT-135) were conducted on the sample to ensure that an alcohol had not been produced (Figures 2.9 and 2.10).

Figure 2.8 ^{13}C NMR Spectrum of Crude Product from the Reaction of *n*-Butylpotassium and Cyclohexene Oxide.

Figure 2.9 ^1H NMR Spectrum of Crude Product from the Reaction of *n*-Butylpotassium and Cyclohexene Oxide.

Figure 2.10 DEPT-135 Spectrum of Crude Product from the Reaction of *n*-Butylpotassium and Cyclohexene Oxide.

2.4.2 Reaction of *n*-Butyllithium and Cyclohexene Oxide

In order to verify that we were obtaining a unique result we compared the product of the *n*-butylpotassium reaction (Scheme 2.6) with the reaction of *n*-butyllithium with cyclohexene oxide (Scheme 1.2). The reaction of *n*-butyllithium with cyclohexene oxide has been studied and is known to produce cyclohex-2-en-1-ol⁶. We ran the reaction of *n*-butyllithium with cyclohexene oxide under the same conditions of the *n*-butylpotassium reaction and obtained a ¹³C NMR spectrum for the reaction product (Figure 2.11). The peak at 74.5 ppm is characteristic of the alcohol functionality associated with the elimination product cyclohexenol. We also observe the pair of peaks at 129.8 and 130.1 ppm which correspond to the unsaturated carbons of the cyclohexenol. We also see a small peak at 212.3 ppm, but it is not the same value as the peak found in the *n*-butylpotassium reaction ¹³C NMR nor does it have the same intensity (Figure 2.8).

Figure 2.11 ¹³C NMR of Crude Product from the Reaction of *n*-Butyllithium with Cyclohexene Oxide.

The ^{13}C NMR spectra clearly indicate that the reaction of *n*-butyllithium with cyclohexene oxide does not produce the same products as the reaction of *n*-butylpotassium with cyclohexene oxide.

2.4.3 Isolation and Analysis of 2-Butylcyclohexanone

Once this had been determined we continued by trying to isolate the product associated with the carbonyl peak from the ^{13}C NMR of the *n*-butylpotassium reaction with cyclohexene oxide (Scheme 2.6). We accomplished this by utilizing radial chromatography on a portion of the reaction sample. We then took the ^{13}C NMR of the first fraction that eluted from the Chromatotron (Figure 2.12).

Figure 2.12 ^{13}C NMR Spectrum of First Fraction Isolated by Radial Chromatography.

The ^{13}C NMR shows nine peaks from 14.0 to 50.7 ppm and one peak at 213.6 ppm that corresponds to a carbonyl carbon. The ^{13}C NMR led us to conclude that the six carbon cyclohexene oxide and the four carbon *n*-butylpotassium had come together in the reaction to produce 2-butylcyclohexanone in a 2% isolated yield (Scheme 2.7). The identity of the compound was confirmed by a comparison to the literature²⁴.

Scheme 2.7 Reaction of *n*-Butylpotassium and Cyclohexene Oxide to Produce 2-Butylcyclohexanone.

Prior to isolation through chromatography, a mass spectrum was obtained for the crude reaction sample (Figure 2.13). The peak at 155.1430 (m/z) corresponds to the calculated mass of 2-butylcyclohexanone $[\text{M}+\text{H}]_{\text{cal}} = 155.14359$ as well as the mass reported in the literature²⁴.

Figure 2.13 Mass Spectrum with Parent Peak for 2-Butylcyclohexanone.

2.4.4 Derivatization of 2-Butylcyclohexanone

In an attempt to further verify our product and increase the isolated yield of the reaction, semicarbazide was added to the crude reaction mixture before evaporation of solvents to give the corresponding semicarbazone in an isolated yield of 10% after recrystallization (Scheme 2.8). The product was then analyzed by ^{13}C NMR (Figure 2.14). The improved isolated yield of the semicarbazone versus underivatized compound may be a consequence of the volatility of 2-butylcyclohexanone as apparent by its spearmint like aroma.

Scheme 2.8 Reaction of 2-Butylcyclohexanone with Semicarbazide to Produce 2-Butylcyclohexanone Semicarbazone.

The ^{13}C NMR of the 2-butylcyclohexanone semicarbazone was calculated using the ^{13}C NMR Predictor Software from ACD Labs (Figure 2.15) and matched the ^{13}C NMR of the recrystallized semicarbazone (Figure 2.14). The melting point of the 2-butylcyclohexanone semicarbazone recrystallized in ethanol was 134°C . Melting points for 2-butylcyclohexanone semicarbazone have been published that range from 138.5°C - 150°C ²⁵⁻²⁸.

Figure 2.14 ^{13}C NMR of 2-Butylcyclohexanone Semicarbazone.

Figure 2.15 Calculated ^{13}C NMR for 2-Butylcyclohexanone Semicarbazone.

2.4.5 Hypothetical Mechanism for Formation of 2-Butylcyclohexanone

Once the identity of our product had been verified to be 2-butylcyclohexanone, a hypothesis on the mechanism of the reaction could be made. Prior to this, we first analyzed the potassium reagent of our reaction to verify that there were no other metals present in the reaction that could be causing some type of oxidation or dehydrogenation because 2-butylcyclohexanone is an oxidized form of our predicted product, *trans*-2-butylcyclohexan-1-ol. We analyzed our potassium reagent, potassium *tert*-amylate, by X-ray Fluorescence (Figure 2.16).

Figure 2.16 X-Ray Fluorescence of Potassium *tert*-Amylate.

The X-ray fluorescence shows a peak for titanium that comes from the stage of the instrument, tungsten that is associated with the source and finally potassium that is in our reagent. We concluded that our sample did not have any other metals present at the level of detection.

Once the purity of our potassium reagent had been verified we continued with the determination of the mechanism that led to the production of the 2-butylcyclohexanone from the reaction of *n*-butylpotassium and cyclohexene oxide. A review of the literature led us to

postulate the following three step mechanism. First, the work done by Hodgson et. al. describes that in the presence of a strong base epoxides can rearrange to enolates through a carbene intermediate²⁹(Scheme 2.9).

Scheme 2.9 Rearrangement of Epoxides to Enolates Through a Carbene Intermediate²⁹.

Second, work conducted by Oku et. al. describes that ketones can be produced when carbenes react with secondary alkoxides by hydride abstraction to produce ketones³⁰(Scheme 2.10).

Scheme 2.10 Reaction of a Secondary Metal Alkoxide with a Carbene to Produce a Ketone³⁰.

Based on the previously described literature, we theorized that we were producing 2-butylcyclohexanone by first opening the epoxide ring of cyclohexene oxide by an S_N2 substitution with *n*-butylpotassium to make the alkoxide of *trans*-2-butylcyclohexan-1-ol as predicted. Next, a second equivalent of *n*-butylpotassium reacted with cyclohexene oxide to produce a carbene alkoxide as postulated by Hodgson. Finally, the carbene alkoxide oxidized the alkoxide of *trans*-2-butylcyclohexan-1-ol to 2-butylcyclohexanone as observed in Oku's chemistry (Scheme 2.11).

Scheme 2.11 Hypothesized Mechanism for the Production of 2-Butylcyclohexanone.

In an attempt to verify the presence of the carbene in the hypothesized mechanism, cyclohexanol was added to the reaction of cyclohexene oxide and *n*-butylpotassium, which is produced by the reaction of *n*-butyllithium with potassium *tert*-amylate. If the carbene was indeed being produced, cyclohexanol should have been converted to cyclohexanone through the reaction of a carbene with the alkoxide of cyclohexanol (Scheme 2.12).

Scheme 2.12 Reaction of *n*-Butylpotassium with Cyclohexene Oxide in the Presence of Cyclohexanol to Produce Cyclohexanone.

Figure 2.17 ^{13}C NMR of Crude Product from the Reaction of *n*-Butylpotassium and Cyclohexene Oxide in the Presence of Cyclohexanol.

After completion of the reaction, ^{13}C NMR was utilized to analyze the distilled product (Figure 2.17). There are two peaks at 213.4 and 212.0 ppm that correspond to the carbonyl functionality. This led us to believe that not only were we producing the carbene but we were converting both the cyclohexanol and the predicted substitution product to ketones. In order to further verify these results we attempted to isolate these compounds utilizing thin layer chromatography, radial chromatography, and gas chromatography without any success. We believe this is due to the fact that these compounds are present in small amounts and are also volatile.

We continued to pursue the verification of the substitution mechanism by reaction of 1-methyl-1,2-epoxycyclohexane with *n*-butylpotassium. The presence of the methyl group at the α -

position should prevent the conversion of the epoxide to a ketone after substitution allowing us to “trap” the substitution product 2-butyl-1-methylcyclohexan-1-ol (Scheme 2.13).

Scheme 2.13 Reaction of 1-Methyl-1,2-Epoxycyclohexane with *n*-Butylpotassium to Produce 2-Butyl-1-Methylcyclohexan-1-ol.

^{13}C NMR analysis was completed on a sample of the product (Figure 2.18). The results of the ^{13}C NMR show a peak at 213.5 ppm which corresponds to a carbonyl functionality. The purity of the 1-methyl-1,2-epoxycyclohexane and deuterated chloroform were verified to make sure that no ketone contaminant was present in these reagents. This ketone may be due to the rearrangement of the corresponding carbene of this epoxide following Hodgson’s mechanism (Scheme 2.14).

Scheme 2.14 Suspected Rearrangement of 1-Methyl-1,2-Epoxycyclohexane to the Corresponding Ketone.

Figure 2.18 ^{13}C NMR of Crude Product from the Reaction of *n*-Butylpotassium with 1-Methyl-1,2-Epoxycyclohexane.

2.4.6 Reaction of *sec*-Butylpotassium and Cyclohexene Oxide

To this point the focus of this work had been on tertiary and primary examples of organopotassium compounds with cyclohexene oxide. We wanted to attempt a reaction with a secondary organopotassium species to see if an epoxide ring opening reaction would occur. We utilized *sec*-butyllithium in order to produce *sec*-butylpotassium (Scheme 2.15) and reacted with cyclohexene oxide to observe its reactivity.

Scheme 2.15 Production of *sec*-Butylpotassium.

Figure 2.19 ^{13}C NMR of Crude Product from the Reaction of *sec*-Butylpotassium and Cyclohexene Oxide.

The reaction product was analyzed utilizing ^{13}C NMR (Figure 2.19). A small peak is formed at 213.1 ppm that corresponds to a carbonyl functionality. The size of the carbonyl peak with relation to the rest of the peaks in the spectrum is small and leads us to believe that the ability to open the epoxide with a secondary carbanion is more difficult because of greater steric interactions.

Chapter 3: Conclusions

Molecular modeling studies of the structure of α -cumylpotassium in the presence of two equivalents of cumene show that the potassium ion interacts with the aromatic rings of the α -cumyl anion and cumene making the benzylic carbon sp^2 hybridized in nature giving the α -cumyl anion an overall flat shape. This makes it easy to react with an electrophile that can come in from either the top or the bottom of the molecule, making the α -cumyl anion a more effective nucleophile (Figure 2.1). Molecular modeling studies done on α -cumyllithium and sodium show that the metal ions interact with the benzylic position making it sp^3 hybridized in nature giving it a tetrahedral geometry that makes it more difficult for an electrophile to react because of steric interactions (Figures 2.2 and 2.3).

The reaction of α -cumylpotassium and cyclohexene oxide produces *trans*-cumylcyclohexanol in high yield in the presence of three equivalents of cumene¹⁶. Based on the molecular modeling studies, we predicted that aromatic solvents such as benzene and *tert*-butylbenzene could effectively substitute cumene to give *trans*-cumylcyclohexanol in high yield but only obtained yields of 3% for the benzene substituted reaction and 27% for the *tert*-butylbenzene substituted reaction (Equations 2.1 and 2.2). The reaction done in the presence of benzene formed a precipitate that was partly the cause of the low yield. It is also possible that both the benzene and *tert*-butylbenzene reactions, which contained only one equivalent of cumene, were terminated too quickly and could have produced higher yields if allowed to react for more than two days as indicated by subsequent kinetic studies.

It was later determined that relatively high yields of *trans*-cumylcyclohexanol could be obtained in the presence of 1.1 or 2.0 equivalents of cumene over time (Tables 2.1 and 2.2), indicating that the high yield of the reaction is not due to the amount of cumene or aromatic

solvent present but to the amount of time that the cumene is allowed to react with *n*-butylpotassium to produce α -cumylpotassium. In other words this was an issue of kinetics. The decrease in yield after a week in the subsequent reactions of α -cumylpotassium could be due to solvent evaporation, introduction of moisture from the air line, or the instability of α -cumylpotassium as observed for α -cumyllithium²² and sodium²³. The next logical step would be to confirm if α -cumylpotassium could be produced then stored in a sealed container and tested periodically to verify its stability. If it can be maintained over long periods of time it could be made commercially available.

The reactivity of a primary organopotassium species, *n*-butylpotassium, with cyclohexene oxide was studied. The reaction did not produce the predicted S_N2 product, *trans*-2-butylcyclohexan-1-ol, but gave 2-butylcyclohexanone (2%). Derivatization to the corresponding semicarbazone further verified the identity of the product and the isolated yield was increased (10%). The formation of 2-butylcyclohexanone was hypothesized to occur by oxidizing the S_N2 product of *n*-butylpotassium and cyclohexene oxide (the alkoxide of *trans*-2-butylcyclohexan-1-ol) with a carbene intermediate produced through the rearrangement of cyclohexene oxide with strong base (*n*-butylpotassium), followed by protection of the ketone product (2-butylcyclohexanone) as its enolate^{29,30} (Scheme 2.11).

Two possible reasons for the low yield: 1) The volatility of 2-butylcyclohexanone and 2) The incomplete isolation of the semicarbazone by recrystallization. More importantly, when we take into consideration that one equivalent of *n*-butylpotassium is used for the formation of the alkoxide of *trans*-2-butylcyclohexan-1-ol, a second equivalent for the creation of the carbene that oxidizes the alcohol to a ketone (2-butylcyclohexanone), and a third equivalent because ketones are easily enolized in the presence of a strong base; it becomes clear that at least three

equivalents of *n*-butylpotassium are necessary and that the highest yield possible in the presence of one equivalent of *n*-butylpotassium would be 33% by the given mechanism (Scheme 2.11).

An attempt was made to verify the formation of a carbene by reacting *n*-butylpotassium and cyclohexene oxide in the presence of the alkoxide of cyclohexanol to make cyclohexanone by carbene oxidation. When potassium *tert*-amylate and *n*-butyllithium were added to a solution of cyclohexene oxide and cyclohexanol two carbonyl peaks were observed through ^{13}C NMR, which could correspond to 2-butylcyclohexanone and cyclohexanone. Unfortunately it was not possible to isolate or quantify the amount of cyclohexanone present. Other alcohol additives should be tested with the goal being their oxidation to suppress the formation of 2-butylcyclohexanone so that *trans*-2-butylcyclohexan-1-ol can be isolated.

Because *n*-butyllithium was confirmed to produce a *beta*-elimination product with cyclohexene oxide (Scheme 1.2⁶ and Figure 2.11) and because the potassium-lithium exchange reaction that produces *n*-butylpotassium is an equilibrium, the reaction of *n*-butylpotassium without any lithium salts should be tested to see if more substitution versus elimination product can be formed.

Verification of the substitution mechanism was also attempted by reacting 1-methyl-1,2-epoxycyclohexane with *n*-butylpotassium to produce the corresponding alcohol, 2-butyl-1-methyl cyclohexan-1-ol. The presence of the methyl group at the α position of the epoxide was predicted to prevent the formation of the ketone but the ^{13}C NMR gave indication of a carbonyl group in the crude reaction mixture. This could be explained by a possible rearrangement mechanism involving the formation of a carbene followed by rearrangement of the methyl group (Scheme 2.14). The carbonyl containing products need to be isolated from both reactions to verify the mechanism. In addition, there may be a difficulty in the reaction regarding the axial

versus the equatorial epoxide bonds as is observed in the preferred axial conformation for the reaction of limonene oxide diastereomers and α -cumylpotassium³¹.

Cyclohexene oxide was reacted with *sec*-butylpotassium and the crude reaction mixture was analyzed by ^{13}C NMR to explore reactions beyond primary alkyl carbanions. The NMR spectrum showed that there was evidence of a carbonyl group but the intensity was extremely low compared to the other peaks in the spectrum. It is also interesting to postulate that if a carbene is being formed and abstracts a hydrogen from an alkoxide, the intermediate dianion could oxidize to cyclohexenol (Scheme 3.1) without requiring a beta elimination mechanism (Scheme 1.2).

Scheme 3.1 Reaction of an Intermediate Dianion with a Carbene to Produce Cyclohexenol.

The findings in this research work give the scientific community another method for substitution of alkyl groups on epoxides without additives. It also gives insight into the differences of reactivity between potassium and other corresponding metals.

Chapter 4: Experimental

4.1 Materials

Potassium *tert*-amylate was generously donated by BASF as K-*tert*-Amylate Solution 15% in cyclohexane. Cumene (98%), cyclohexene oxide (98%), *n*-butyllithium (2.5 M in hexanes), *sec*-butyllithium (1.3 M in hexanes), benzene, *tert*-butylbenzene (99%), dichloromethane (99.6%), hexanes (98.5% CHROMASOLV), and 2-propanol (99.9% CHROMASOLV) were purchased from the Sigma-Aldrich Company. Sodium Acetate was purchased from the Spectrum Chemical Manufacturing Corporation. Semicarbazide Hydrochloride was purchased from Mallinckrodt Incorporated. 1-Methyl-1,2-Epoxy cyclohexane was purchased from TCI America.

4.2 Equipment

4.2.1 Rotary Evaporator

The Buchi R-110 Rotovapor rotary evaporator from BUCHI, LABORATORLUMS-TECKNIK AG, 70 Switzerland was utilized to remove volatile solvents from reaction mixtures.

4.2.2 Horizontal Distillation

The Kuelgrohr Horizontal Distillation Set-Up was utilized to remove high-boiling point solvents from reaction samples after using the rotary evaporator.

4.2.3 Chiral Column High Performance Liquid Chromatography

Chiral Column High Performance Liquid Chromatography was utilized to quantify and identify TCC. A Chiralcel OJ column from Diacel Chemical Industries Inc. was employed. A Spectra-Physics Spectra System P1500 gradient pump was utilized with a 95%/5% hexanes/2-

proponal mobile phase mixture. The UV2000 detector was set at 215 nm to avoid overlap with other compounds observed at 256 nm. Samples of 1-3 μL were injected at room temperature.

4.2.4 Radial Chromatography and UV Light

Radial chromatography was utilized to separate crude reaction samples. A solution of 5% ethyl acetate and 95% hexanes was used to moisten the plate and as the mobile phase. An aliquot of approximately 0.25 g was introduced to the $\frac{1}{4}$ inch silica plate as it rotated. The UVGL-15 Mineralight® multiband UV 254/366 nm (115 V, 60 Hz, 0.16 amps) lamp was utilized to observe the product band as it eluded from the center to the outside of the plate.

4.2.5 Melting-Point Apparatus

A Mel-Temp® Electrothermal® melting-point apparatus was utilized to determine the melting point of isolated products packed to a height of at least 3mm in melting point tubes. An un-calibrated Celsius mercury thermometer was utilized to measure the temperature.

4.2.6 Nuclear Magnetic Resonance (NMR)

A Bruker-Spectrospin 300 MHz NMR was utilized to obtain Carbon-13 (^{13}C), Proton (^1H), and Distortionless Enhancement by Polarization Transfer-135° (DEPT-135) spectrum of crude reaction samples and isolated products. Deuterated chloroform (CDCl_3) with tetramethylsilane was utilized as the solvent for the NMR sample.

4.2.7 Mass Spectrometer

The JEOL AccuTOF JMS-T100LC and Direct Analysis in Real Time (DART) Ion Sense in positive ion mode $[\text{M}+\text{H}]^+$ were utilized to obtain the mass spectrum of the crude reaction mixture containing 2-butylcyclohexanone.

4.3 Experimental

4.3.1 Attempted Synthesis of *trans*-Cumylcyclohexanol in the Presence of Benzene

To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 10 mL of 1.2 M potassium *tert*-amylate (12 mmol), 1.4 mL of cumene (10 mmol), and 2.7 mL of benzene (30 mmol) via syringe under nitrogen gas. To the flask was added 5 mL of 2.5 M *n*-butyllithium (12.5 mmol) dropwise to remove all traces of moisture as indicated by a color change. After two days, the reaction formed a brown precipitate and 1 mL of cyclohexene oxide (10 mmol) was added dropwise. The reaction was stirred a further two hours becoming dark. 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and the combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator and the remaining yellow oil was distilled bulb to bulb. Chiral column High Performance Liquid Chromatography (HPLC) was performed on the distillate to identify and quantify the percent yield of TCC as follows: to a 15 mL volumetric flask was added 0.600 g of crude sample and hexanes. 3 μ L of this solution was injected into the HPLC with a mobile phase of 95% hexanes to 5% isopropanol and a velocity of 1 mL/ min. A wavelength of 215 nm was used for the measurement because at 256 nm the enantiomer areas were not equal indicating overlap of other products with the second peak. A standard solution was prepared using 0.122 g of purified TCC added to a 10 mL volumetric flask that was then filled to the line with hexanes. 1 μ L of this solution was analyzed by HPLC. Once the HPLC results for TCC synthesized with benzene solvent and the standard were obtained, dimensional analysis was utilized to determine that the percentage yield was 3%.

4.3.2 Attempted Synthesis of *trans*-Cumylcyclohexanol in the Presence of *tert*-butylbenzene

Two equivalents *tert*-butylbenzene (20 mmol) were used in the same reaction sequence as previously described for benzene. HPLC analysis was performed on a sample of 0.134g of the *tert*-butylbenzene derived TCC and hexanes in a 10 mL volumetric flask.

4.3.3 Synthesis of *trans*-Cumylcyclohexanol with 1.1 Equivalents of Cumene

Day 2. To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 10 mL of 1.2 M potassium *tert*-amylate (12 mmol) and 1.5 mL of cumene (11 mmol) via syringe under nitrogen gas. To the flask was added 4 mL of 2.5 M *n*-butyllithium (10 mmol) dropwise to remove all traces of moisture as indicated by a color change. After two days, the reaction formed a brown precipitate and 1 mL of cyclohexene oxide (10 mmol) was added dropwise. The reaction was stirred a further two hours becoming dark. 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and the combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator and the remaining yellow oil was distilled bulb to bulb utilizing a Kugelrohr apparatus to give 1.05 g (49%) of crude product as viscous oil.

Day 4. The reaction was set up in the same manner as the Day 2 experiment. After four days cyclohexene oxide was added (10 mmol). The work up was performed as previously described to give 1.44 g (67%) of crude product as viscous oil.

Day 6. The reaction was set up in the same performed as the Day 2 experiment. After six days cyclohexene oxide was added (10 mmol). The work up was performed as previously described to give 1.47 g (68%) of crude product as viscous oil.

Day 8. The reaction was set up in the same manner as the Day 2 experiment. After eight days cyclohexene oxide was added (10 mmol). The work up was performed as previously described to give 1.58 g (74%) of crude product as viscous oil.

Day 10. The reaction was set up in the same manner as the Day 2 experiment. After ten days cyclohexene oxide was added (10 mmol). The work up was performed as previously described to give 1.44 g (67%) of crude product as viscous oil.

4.3.4 Synthesis of *trans*-Cumylcyclohexanol with 2.0 Equivalents of Cumene

Day 1. To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 10 mL of 1.2 M potassium *tert*-amylate (12 mmol) and 2.25 g of cumene (18.8 mmol) via syringe under nitrogen gas. To the flask was added 4 mL of 2.5 M *n*-butyllithium (10 mmol) dropwise to remove all traces of moisture as indicated by a color change. After one day, the reaction formed a brown precipitate and 0.88 g of cyclohexene oxide (9.88 mmol) was added dropwise. The reaction was stirred a further two hours becoming dark. 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and the combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator and the remaining yellow oil was distilled bulb to bulb utilizing a Kugelrohr apparatus to give 1.27 g (65%) of crude product as viscous oil.

Day 2. To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 10 mL of 1.2 M potassium *tert*-amylate (11.5 mmol) and 2.30 g of cumene (19.2 mmol) via syringe under nitrogen gas. To the flask was added 4.6 mL of 2.5 M *n*-butyllithium (12 mmol) dropwise to remove all traces of moisture as indicated by a color change. After two days, the reaction formed a brown precipitate and 0.99 g of cyclohexene oxide (10.1 mmol) was added dropwise. The reaction was stirred a further two hours becoming dark. 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and the combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator and the remaining yellow oil was distilled bulb to bulb utilizing a Kugelrohr apparatus to give 1.55 g (71%) of crude product as viscous oil.

Day 4. The reaction was set up in the same manner as the Day 2 experiment. After four days 0.99 g of cyclohexene oxide (10.1 mmol) was added dropwise. The work up was performed as previously described to give 1.57 g (71%) of crude product as viscous oil.

Day 6. To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 10 mL of 1.2 M potassium *tert*-amylate (12 mmol) and 2.32 g of cumene (19.3 mmol) via syringe under nitrogen gas. To the flask was added 4.8 mL of 2.5 M *n*-butyllithium (12 mmol) dropwise to remove all traces of moisture as indicated by a color change. After six days, the reaction formed a brown precipitate and 0.99 g of cyclohexene oxide (10.1 mmol) was added dropwise. The reaction was stirred a further two hours becoming dark. 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and the

combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator and the remaining yellow oil was distilled bulb to bulb utilizing a Kugelrohr apparatus to give 1.51 g (69%) of crude product as viscous oil.

Day 8. The reaction was set up in the same manner as the Day 6 experiment. After eight days 0.99 g of cyclohexene oxide (10.1 mmol) was added dropwise. The work up was performed as previously described to give 1.58 g (72%) of crude product as viscous oil.

Day 10. The reaction was set up in the same manner as the Day 2 experiment. After ten days 1.04 g of cyclohexene oxide (10.6 mmol) was added dropwise. The work up was performed as previously described to give 1.33 g (57.8%) of crude product as viscous oil.

4.3.5 Synthesis of 2-Butylcyclohexanone

To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 40 mL of 1.2 M potassium *tert*-amylate (48 mmol) and 16 mL of 2.5 M *n*-butyllithium (40 mmol) dropwise via syringe under nitrogen gas. After fifteen minutes, the reaction formed a white precipitate and 3.74 g of cyclohexene oxide (38.1 mmol) was added dropwise. The reaction was stirred a further two hours then 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and the combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator and the remaining light yellow oil was distilled bulb to bulb utilizing a Kugelrohr apparatus to give 1.18 g of crude product. Radial Chromatography was performed on the distillate to identify and quantify the percent yield of 2-butylcyclohexanone as follows: A 5% ethyl acetate/hexane solution was prepared and utilized to

moisten the ¼ inch rotating silica plate. To the moistened silica plate was added 0.28 g of crude sample. An Ultraviolet light was utilized to observe and collect the first band as it eluted from the plate. The solvent was evaporated utilizing aspirator pressure giving 0.03 g (2%) of isolated product. The ¹H NMR, ¹³C NMR and Mass Spectrum Analysis coincide with the literature¹².

4.3.6 Synthesis of 2-Butylcyclohexanone Semicarbazone

To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 10 mL of 1.2 M potassium *tert*-amylate (12 mmol) and 0.99 g of cyclohexene oxide (10.1 mmol) via syringe under nitrogen gas. To the flask was added 4 mL of 2.5 M *n*-butyllithium (10 mmol) dropwise. The reaction was stirred further 1 hour then 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with hexane (3x 30mL) and the combined organic layers were poured into a 250 mL round bottom flask. To the flask was added 1.57 g of sodium acetate and 0.98 g semicarbazide and shaken vigorously until a white solid formed. The remaining solvent was evaporated via vacuum distillation on a rotary evaporator and the remaining light yellow oil was allowed to cool until crystals formed. The remaining crystals were then washed with cold ethanol to give 0.19 g of semicarbazone or 0.154 g 2-butylcyclohexanone (10%). The semicarbazone was recrystallized using ethanol to give fine white crystals: mp. 134° C (lit. mp. 138.5-139.5° C) ¹³C NMR (CDCl₃) δ= 14.105, 22.867, 23.754, 25.144, 26.306, 29.458, 30.700, 33.018, 43.996, 155.652, 157.915.

4.3.7 Attempted Synthesis of Cyclohexanone

To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 1 mL of cyclohexanol (10 mmol), 2 mL of cyclohexene oxide (20 mmol), 24 mL of 1.2 M potassium *tert*-amylate (24 mmol) via syringe under nitrogen gas. To the flask was added

8 mL of 2.5 M *n*-butyllithium (20 mmol) dropwise. The reaction was stirred further 1 hour then 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and the combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator to give the remaining crude product as a viscous slightly yellow oil.

4.3.8 Attempted Synthesis of 2-Butyl-1-Methylcyclohexan-1-ol

To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 10 mL of 1.2 M potassium *tert*-amylate (12 mmol) and 1.2 mL of 1-methyl-1,2-epoxycyclohexane (9.96 mmol) via syringe under nitrogen gas. To the flask was added 4 mL of 2.5 M *n*-butyllithium (10 mmol) dropwise. The reaction was stirred further 1 hour then 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and the combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator to give the remaining crude product as a viscous yellow oil.

4.3.9 Reaction of *sec*-Butylpotassium and Cyclohexene Oxide

To a clean and dry 100 mL round bottom flask, with magnetic stir bar, and rubber septum was added 10 mL of 1.2 M potassium *tert*-amylate (12 mmol) and 1.0 mL of cyclohexene oxide (9.88 mmol) via syringe under nitrogen gas. To the flask was added 7.6 mL of 2.5 M *sec*-butyllithium (9.88 mmol) dropwise. The reaction was stirred further 1 hour then 30 mL of de-ionized water were added and the yellow organic layer was washed with more water (2x 30mL). The combined aqueous layers were extracted with dichloromethane (3x 30mL) and

the combined organic layers were dried over potassium carbonate and decanted into a round bottom flask. The solvent was removed via vacuum distillation on a rotary evaporator to give the remaining crude product as a viscous yellow oil.

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Curriculum Vitae

Christina was born in El Paso, Texas to Raul Ruben and Maria Cristina Alvarado. She graduated from Riverside High School, El Paso, Texas in the spring of 2003. She attended the University of Texas at El Paso (UTEP) in the fall of 2003 with generous support from the Ysleta Education Foundation Scholarship and the UTEP Presidential Excellence Scholarship. She graduated Magna Cum Laude with a Bachelor of Science degree in chemistry in the spring of 2007. Christina entered the UTEP Chemistry Ph.D program that fall. During her first year of graduate study she worked as a teaching assistant instructor for the organic chemistry lab and began work as a research assistant in the lab of her advisor Dr. James M. Salvador. She received generous support from the Louis Stokes Alliance for Minority Participation Bridge to the Doctorate Fellowship and UTEP Graduate School. She has presented her work at the American Chemical Society (ACS) 239th National Meeting, San Francisco, California and the ACS 65th Southwest Regional Meeting, El Paso, Texas. She has also presented her work at the Society for Advancement of Chicanos and Native Americans in Science (SACNAS) University of Texas at El Paso Chapter Conference, El Paso, Texas.

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