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RECENT ADVANCES IN THE CHEMISTRY AND SYNTHETIC USES OF MAGNESIUM CARBENOIDS

Tsuyoshi Satoh*

Graduate School of Chemical Sciences and Technology, Tokyo University of Science; Ichigaya-funagawara-machi 12, Shinjuku-ku, Tokyo 162-0826, Japan
tsatoh@rs.kagu.tus.ac.jp

Abstract – Carbenes and carbenoids have long been recognized to be a highly reactive species and are frequently used as intermediates in organic synthesis. However, most of the carbenes and carbenoids are relatively short-lived and are too reactive to control. Recently, the author’s group found that the treatment of aryl α-chloroalkyl sulfoxides and α-chlorovinyl *p*-tolyl sulfoxides with a Grignard reagent at low temperature gave magnesium carbenoids via the sulfoxide-magnesium exchange reaction. Magnesium carbenoids, cyclopropylmagnesium carbenoids, cyclobutylmagnesium carbenoids, magnesium alkylidene carbenoids, and magnesium β-oxido carbenoids were generated from the corresponding α-chloro sulfoxides with a Grignard reagent at low temperature. The generated magnesium carbenoids were proved to be relatively stable and they showed very interesting reactivity with several nucleophiles to afford many unprecedented new reactions. The present review is written for the purpose of reflecting recent achievements in the areas of chemistry and synthetic application of above-mentioned magnesium carbenoids. This review mainly covers literature from 2006 to late 2011.

CONTENTS

1. INTRODUCTION

Synthetic organic chemistry is a base of medicinal chemistry and a variety of chemical sciences. The exploitation of new methods for carbon-carbon and carbon-heteroatom bond-formation is of most importance in synthetic organic chemistry. Carbenes **1** and carbenoids **2a** have long been known to be highly reactive carbon species that show a variety of unique reactions such as dimerization to give olefins, addition to olefins to give cyclopropanes, ylide formation, and rearrangement.[1] The carbon-hydrogen insertion (CH insertion) reaction and carbon-carbon insertion (CC insertion) reaction are one of the most striking reactions of carbenes and carbenoids.[2] The CH and CC insertion reactions are very interesting and highly important for the construction of molecules, because the reactions enable the formation of carbon-carbon bonds between a carbene (or carbenoid) carbon and an unactivated carbon.

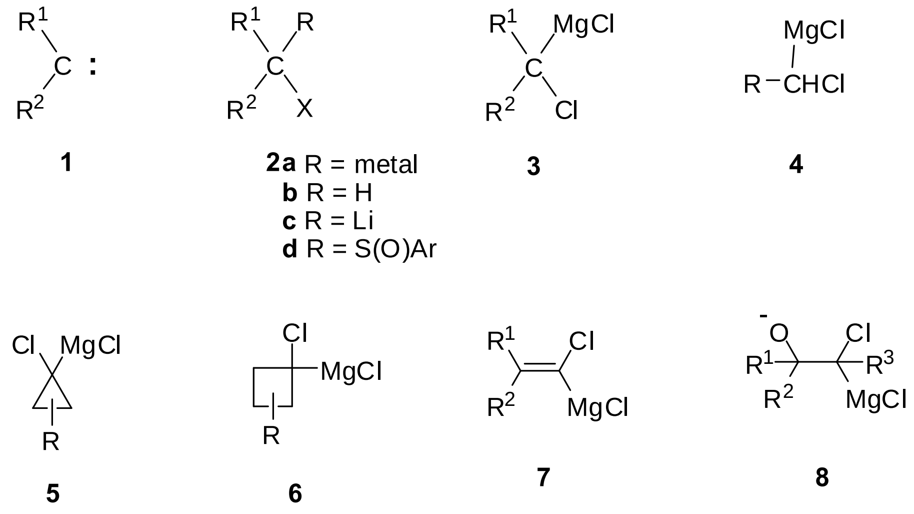


Figure 1. Carbenes, Carbenoids and Magnesium Carbenoids

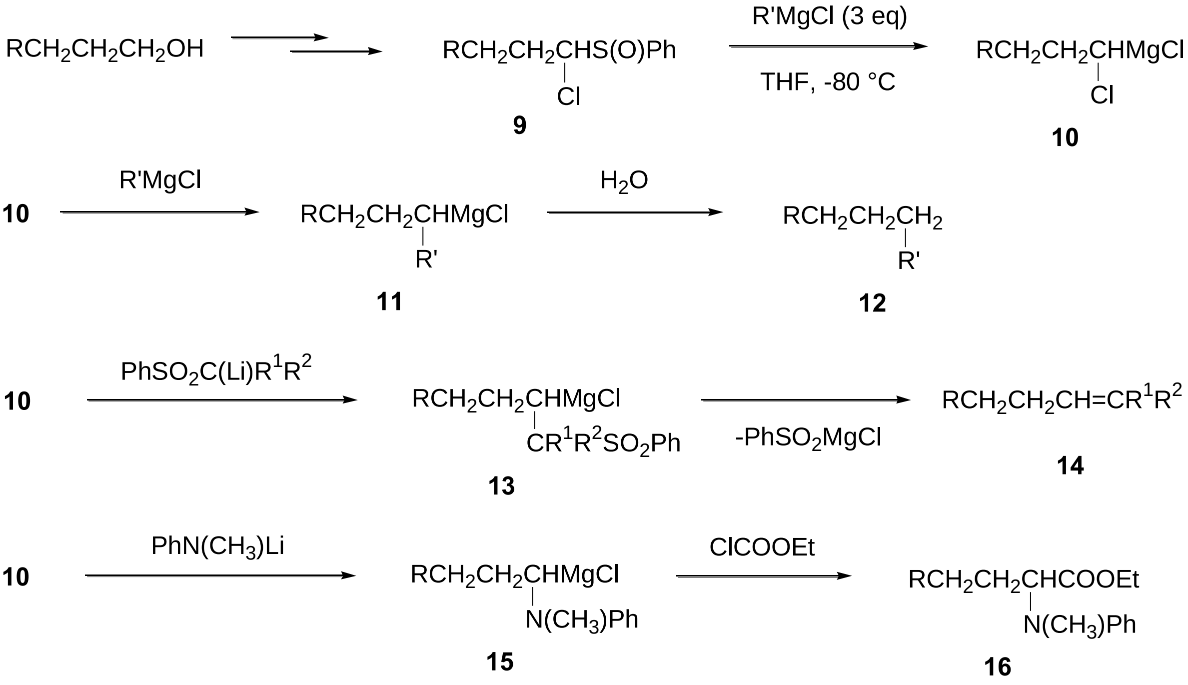
As mentioned above, carbenes **1** and carbenoids **2a** are quite unique and important reactive carbon species in carbon-carbon and carbon-heteroatom bond-formation; however, those reactive species are not fully used in organic synthesis. The reasons are as follows. One is that the precursors for the generation of carbenes and carbenoids are quite limited. The other is that the reactivity of the species is usually too high to control. In order to solve the problem mentioned above, we used aryl α-haloalkyl (or alkenyl) sulfoxides **2d** as the precursors, instead of haloalkanes **2b**, and used sulfoxide-magnesium exchange reaction[3] for generation of much mild (in contrast to lithium carbenoid **2c**) magnesium carbenoids **3**. It is worth noting that many aryl α-chloroalkyl (or alkenyl) sulfoxides **2d** are quite easily synthesized in high overall yields. Magnesium carbenoids **4**, cyclopropylmagnesium carbenoids **5**, cyclobutylmagnesium carbenoids **6**, magnesium alkylidene carbenoids **7**, and magnesium β-oxido carbenoids **8** were generated at low temperature from the corresponding sulfoxides with a Grignard reagent in high to quantitative yields. They were found to be stable usually at below -60 °C for at least 30 min. These magnesium carbenoids have their own unique reactivity and we have found many unprecedented reactions from the reactive species. Recent advances in the chemistry and synthetic uses of magnesium carbenoids are described in this review.

2. MAGNESIUM CARBENOIDS

2-1. Reaction with *N*-Lithio Arylamines

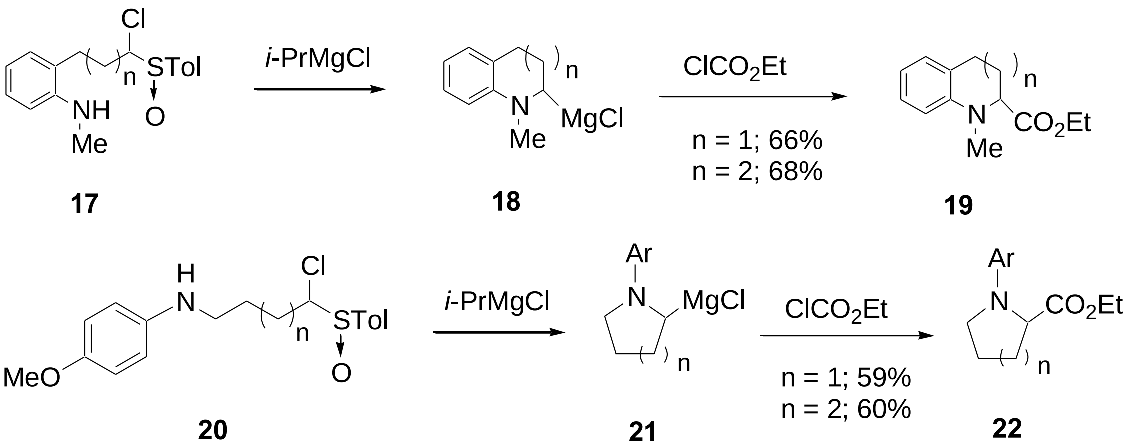
In 2004, the author's group reported the generation of magnesium carbenoids **10** from 1-chloroalkyl phenyl sulfoxides **9** with a Grignard reagent in THF at low temperature in quantitative yields (Scheme 1).[5] Magnesium carbenoids **10** were proved to be stable at lower than -60 °C for over 30 min. When this reaction was conducted with excess Grignard reagent with warming the temperature of the reaction mixture to -30 °C, magnesium carbenoids **10** reacted with the Grignard reagent to afford alkylated alkylmagnesium chlorides **11**, which gave alkanes **12** in good yields by treatment with water. This result showed us that magnesium carbenoid **10** is highly electrophilic species. Treatment of magnesium carbenoids **10** with lithium α-sulfonyl carbanions gave olefins **14** in good to high yields via alkylated intermediates **13**.[5]

Very interesting result was obtained from the reaction of magnesium carbenoid **10** with *N*-lithio arylamines. Thus, the reaction of **10** with *N*-lithio *N*-methylaniline initially afforded *N*-alkylaniline having carbanion at the α-position **15** in over 80% yield. This carbanion was able to be trapped with ethyl chloroformate to give α-amino acid ester **16** in good yield.[6] It is worth noting that α-amino acid esters **16** were synthesized in over 70% yields starting from **9** in one-pot.



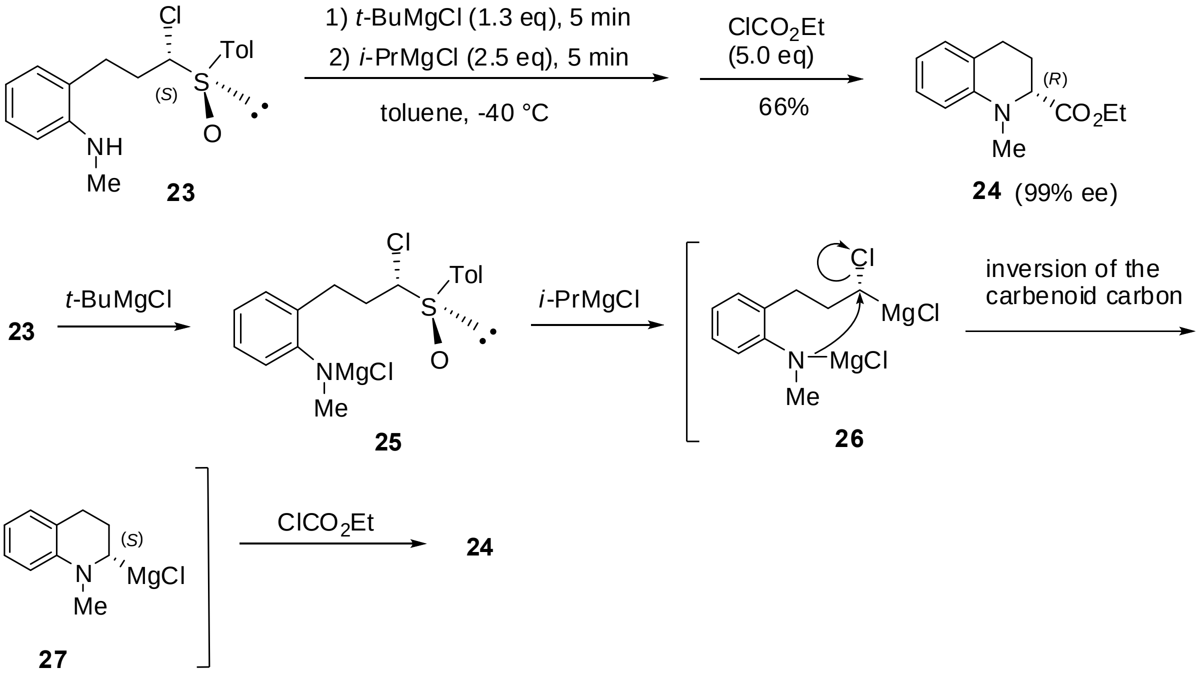
Scheme 1. Generation of Magnesium Carbenoids **10** and Reaction with Nucleophiles Followed by Electrophiles

In continuation of our interest in the synthesis, including asymmetric synthesis, of α-amino acids, above-mentioned chemistry was extended to intramolecular reaction and the results are summarized in Scheme 2. Thus, treatment of 1-chloroalkyl *p*-tolyl sulfoxide having a 2-aminophenyl group at the ω-position **17** with *i*-PrMgCl followed by ethyl chloroformate gave cyclic α-amino acid derivative **19** (n=1 and 2) through α-amino-substituted alkylmagnesium intermediate **18** in up to 68% yield. On the other hand, treatment of 1-chloroalkyl *p*-tolyl sulfoxide having an arylamino group at the ω-position **20** with *i*-PrMgCl followed by ethyl chloroformate gave proline derivative **22** (n=1) in 59% yield and pipecolic acid derivative **22** (n=2; 60% yield) through α-amino-substituted alkylmagnesium intermediates **21** (Scheme 1).[7]



Scheme 2. Intramolecular Reaction of Magnesium Carbenoids with Nitrogen Nucleophiles Followed by Ethyl Chloroformate giving Cyclic α-Amino Acid Esters **19** and **22**

In order to investigate if the above-mentioned procedure could be expanded to an asymmetric synthesis of cyclic α-amino acid derivatives and to investigate the stereochemistry of the key reaction, we tried the procedure with optically active starting material (Scheme 3).[8]

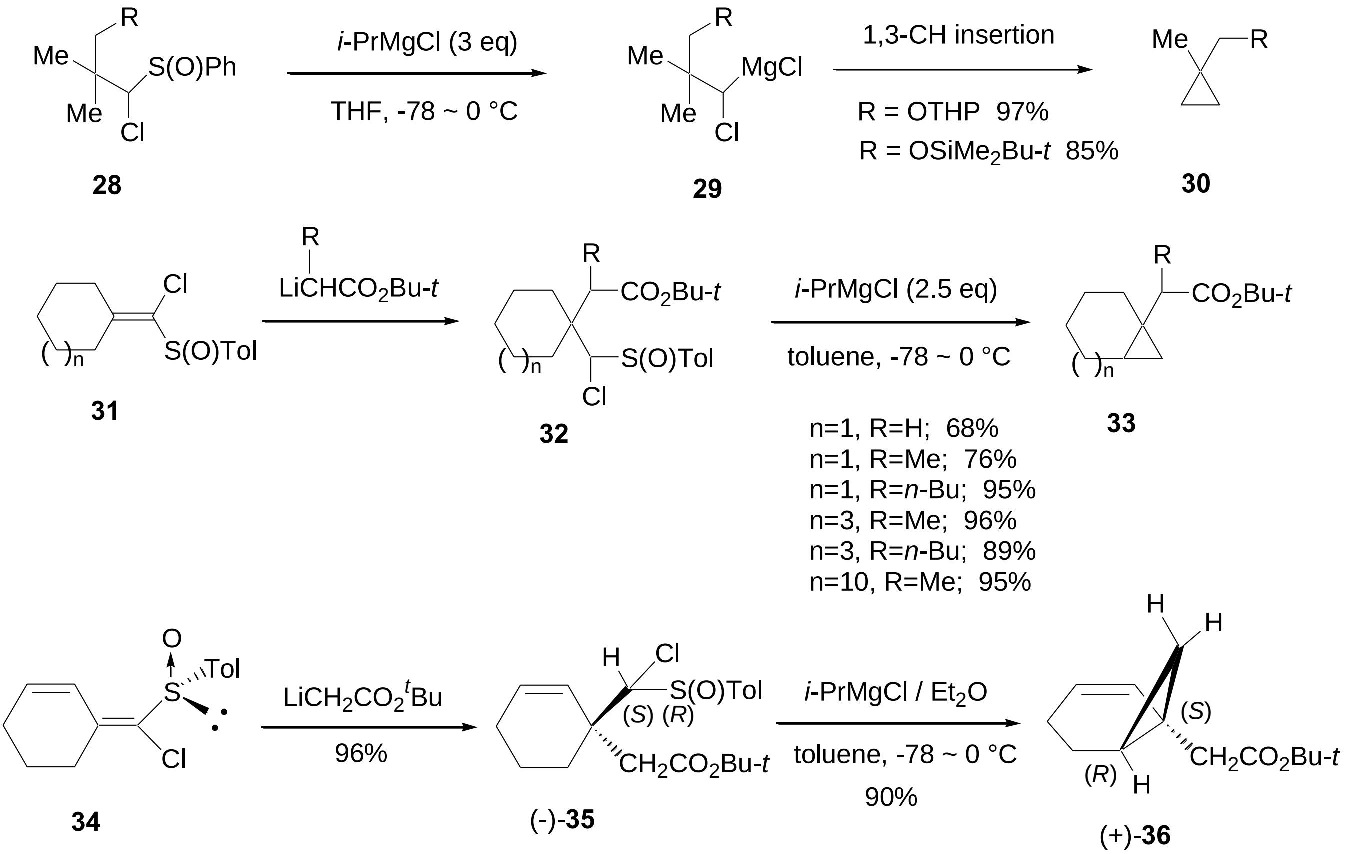


Scheme 3. Asymmetric Synthesis of Cyclic α-Amino Acid (Pipecolic Acid Derivative) **24** from Enantiopure 1-Chloroalkyl *p*-Tolyl Sulfoxide **23**

At first, enantiopure starting material, (1*S*,R_S)-1-chloro-3-(2-methylaminophenyl)propyl *p*-tolyl sulfoxide **23** was synthesized from oxindole. 1-Chloroalkyl *p*-tolyl sulfoxide **23** is a crystalline compound and the absolute configuration was determined by X-ray crystallographic analysis. Enantiopure 1-chloroalkyl-*p*-tolyl sulfoxide **23** was treated with *t*-BuMgCl followed by *i*-PrMgCl and ethyl chloroformate as described above to give the optically active pipecolic acid derivative **24** in 66% yield (Scheme 3). The optical yield was mearsured by chiral stationary column and found that it was over 99%. The high enantiomeric excess of product **24** means that almost no racemization occurred throughout the reactions. The absolute configuration of **24** was determined to be (*R*)-1-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid ethyl ester.[8] With absolute configuration of **24** in hand, the whole stereochemistry of the reaction can be inferred as shown in Scheme 3. At first, treatment of **23** with *t*-BuMgCl resulted in the formation of magnesium amide **25**. As sulfoxide-magnesium exchange reaction is known to take place with retention of the configuration of the carbon bearing the sulfinyl group, sulfoxide **25** gave magnesium carbenoid having *S*-absolute configuration **26**. The key intramolecular reaction proceeds with inversion of the carbenoid carbon to afford α-amino carbanion having *S*-absolute configuration **27**. Finally, the anion was trapped by ethyl chloroformate with retention of the configuration of the carbanion to afford the final product **24**.

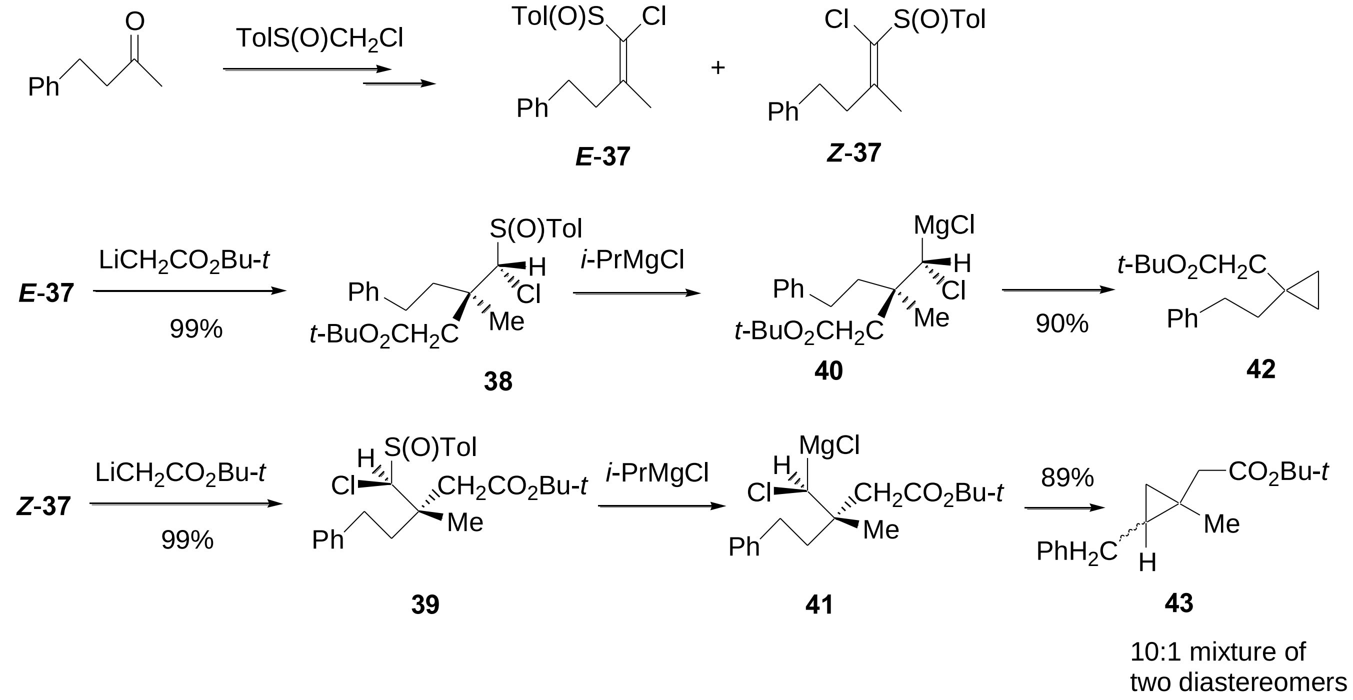
2-2. 1,3-Carbon Hydrogen (1,3-CH) Insertion Reaction

As mentioned in the introduction, CH insertion reaction is quite interesting and useful reaction for construction of molecules.[2] Author's group studied the CH insertion reaction of magnesium carbenoids starting with 1-chloroalkyl phenyl sulfoxides **28** as representative examples (Scheme 4). Thus, **28** was treated with three equiv of *i*-PrMgCl in THF at -78 °C and the reaction mixture was slowly allowed to warm to 0 °C to result in the formation of cyclopropanes **30** in good to high yields.[9] The intermediate of this reaction was proved to be magnesium carbenoid **29** and 1,3-CH insertion reaction exclusively took place between methyl-carbon and the carbenoid carbon to afford **30** as the sole product. As recognized from the results, the 1,3-CH insertion reaction of magnesium carbenoids gives high yield of cyclopropanes and the conditions of the reaction are quite mild.



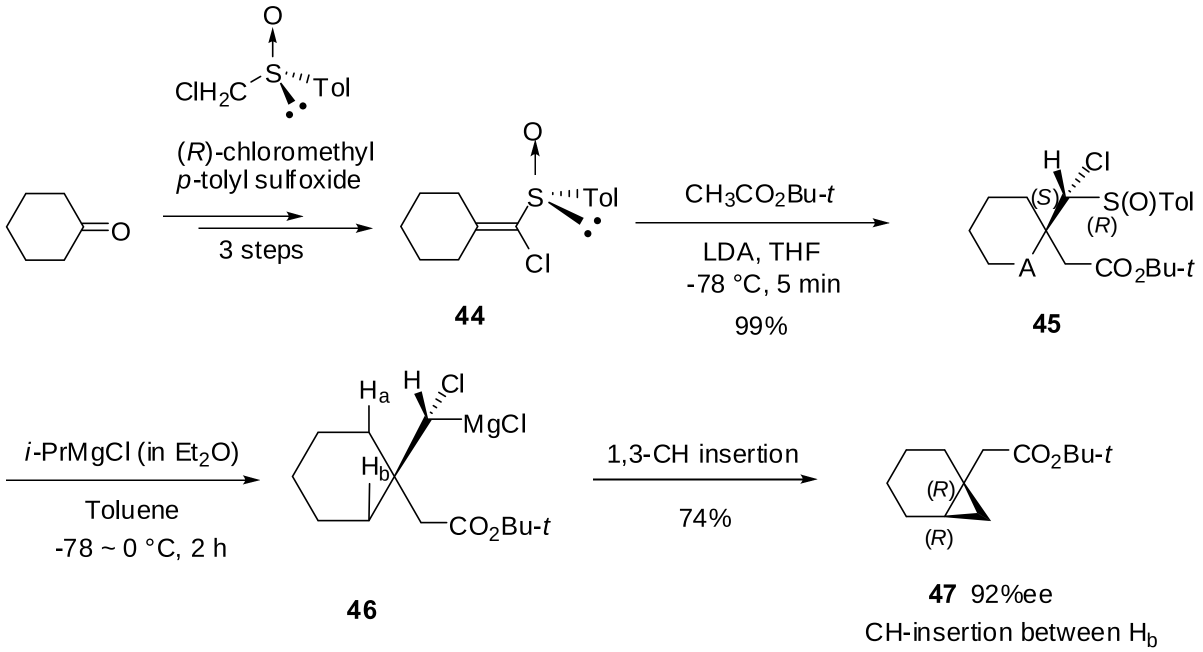
Scheme 4. 1,3-CH Insertion of Magnesium Carbenoids Giving Cyclopropanes

The same 1,3-CH insertion reaction was found to proceed with sulfoxides **32**, which were derived from vinyl sulfoxides **31** with lithium enolate of carboxylic acid *tert*-butyl ester in high yields.[10] Thus, treatment of sulfoxides **32** with 2.5 equiv of *i*-PrMgCl in toluene resulted in the formation of bicyclo[n.1.0]alkanes **33** in high to quantitative yields. This type of reaction can be realized not only with *tert*-butyl ester but also with amides.[11] Asymmetric synthesis of enantiopure bicyclo[4.1.0]hept-2-ene having acetic ester moiety on the bridgehead carbon **36** was realized from enantiopure α-chloro vinyl sulfoxide **34**, which was synthesized from 2-cyclohexenone and (*R*)-chloromethyl *p*-tolyl sulfoxide.[11] The addition reaction of lithium enolate of *tert*-butyl acetate to **34** gave (-)-**35** in almost quantitative yield with perfect selectivity. Treatment of **35** with *i*-PrMgCl in toluene resulted in the formation of enantiopure **36** in 90% yield. The 1,3-CH insertion reaction proceeded only on sp^3 carbon.



Scheme 5. Regiospecific Magnesium Carbenoid 1,3-CH Insertion Reaction

The 1,3-CH insertion of magnesium carbenoids bearing *tert*-butyl ester at the β-position was found to be highly regiospecific.[12] Thus, geometrical isomers of vinyl sulfoxides, ***E*-37** and ***Z*-37**, were synthesized form 4-phenyl-2-butanone in high overall yields. Addition reaction of these vinyl sulfoxides with lithium enolate of *tert*-butyl acetate gave adducts **38** and **39**, respectively, in quantitative yields. Adducts **38** and **39** were both single isomers and diastereomers to each other. The adducts were treated with *i*-PrMgCl in toluene at -78 °C and the temperature of the reaction mixture was slowly allowed to warm to 0 °C. Interestingly, the treatment of **38** with *i*-PrMgCl gave cyclopropane **42** in 90% yield without any contamination of cyclopropane **43**. On the contrary, the same reaction of **39** afforded cyclopropane **43** in 89% yield without any trace of cyclopropane **42**. Namely, the 1,3-CH insertion of adduct **38** took place between the carbenoid carbon of **40** and the methyl carbon to give **42**. The 1,3-CH insertion reaction of the adduct derived from ***Z*-37** took place between the carbenoid carbon and the methylene carbon to give **43** with high regiospecificity via magnesium carbenoid **41** (Scheme 5). The stereochemistry of **38** and **39**, and the mechanism and origin of this regiospecificity are discussed in the original paper.[12,13]



Scheme 6. 1,3-CH Insertion Reaction of Chiral Magnesium Carbenoid **46** Derived from Adduct **45** with *i*-PrMgCl to Give Optically Active Bicyclo[4.1.0]heptane Derivative **47**

Asymmetric synthesis of bicyclo[n.1.0]alkanes by the enantioselective 1,3-CH insertion reaction of chiral magnesium carbenoids was also realized (Scheme 6).[14] Thus, optically pure 1-chlorovinyl *p*-tolyl sufoxide **44**, derived from cyclohexanone and (*R*)-chloromethyl *p*-tolyl sulfoxide, was treated with lithium enolate of *tert*-butyl acetate. This reaction gave adduct **45** in quantitative yield; however, about 7% yield of diastereomer was observed. The main adduct was separated and treated with *i*-PrMgCl to afford optically active bicyclo[4.1.0]heptane bearing a *tert*-butyl acetate moiety **47** in 74% yield. Absolute stereochemistry and enantiomeric excess were determined from 3,6-dibromocarbazole derivative of **47** and *ee* was found to be 92%. With both absolute configuration of **46** and **47** in hand, it was concluded that the 1,3-CH insertion reaction proceeded between the C-H$_b$ bond. From the results, we concluded that the 1,3-CH insertion reaction of chiral magnesium carbenoid bearing a *tert*-butyl carboxylate proceeds with high enantioselectivity.

A plausible mechanism of this enantioselective magnesium carbenoid 1,3-CH insertion reaction is proposed as shown in Figure 2.[14] Because the sulfoxide-magnesium exchange reaction is known to take place with retention of the configuration of the carbon bearing the sulfinyl group, treatment of **45** with *i*-PrMgCl gives magnesium carbenoid having *S*-configuration **46**. The magnesium and carbonyl oxygen atom of the *tert*-butyl ester group make six-membered intermediate, in which the bulky *tert*-butoxy group would occupy equatorial position. Carbon-hydrogen(H$_b$) bond of the methylene attacks from rear of the carbon-chlorine bond to give **47**. On the other hand, as the carbon-hydrogen(H$_a$) bond of the methylene is placed almost vertically to the carbon-chlorine bond, the 1,3-CH insertion reaction hardly takes place and **Ent-47** is rarely produced.

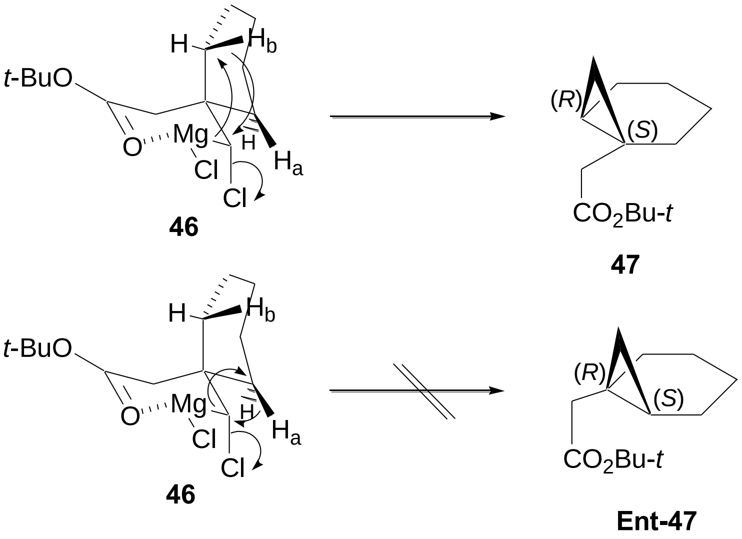
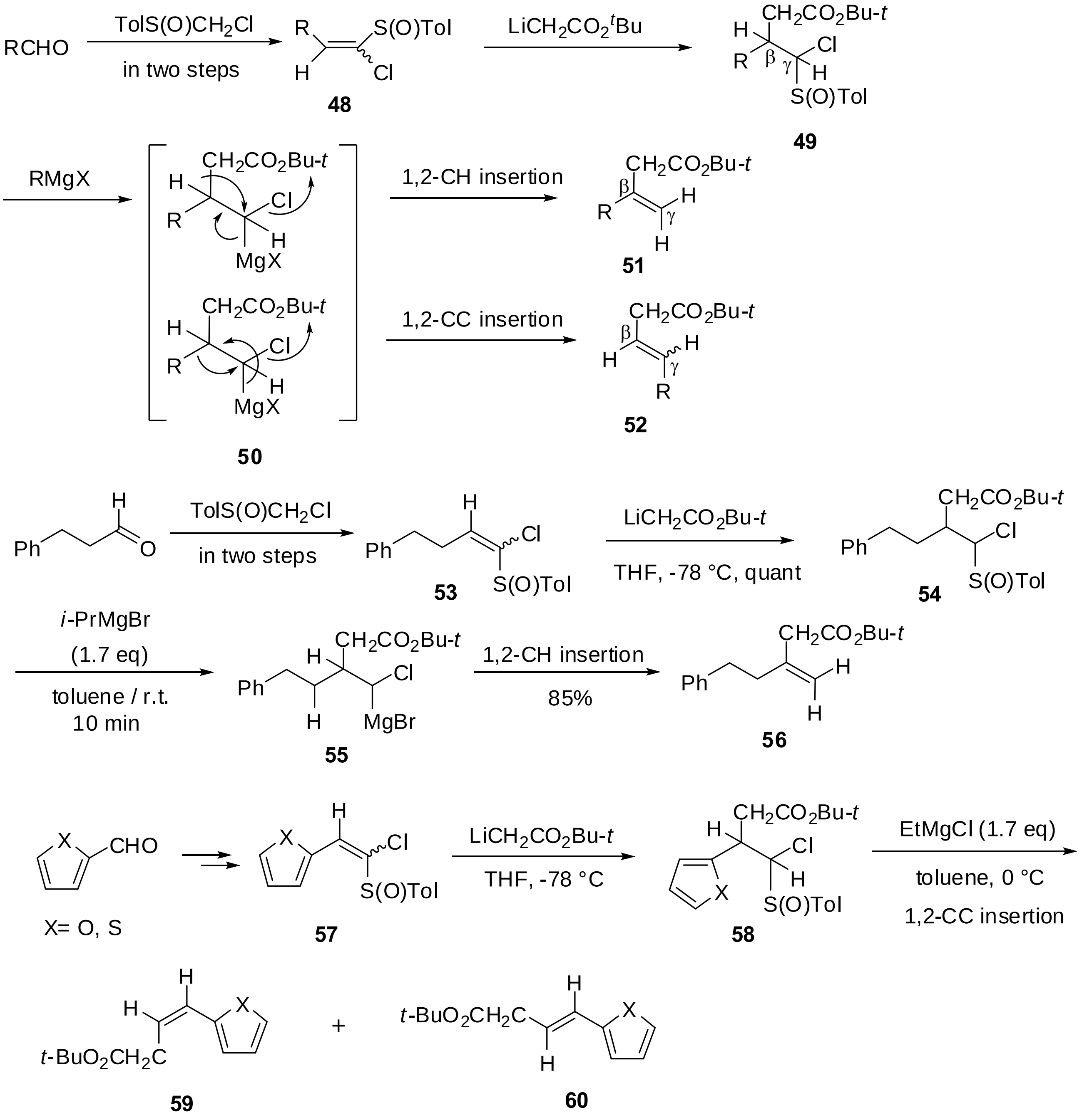


Figure 2. Mechanism for the Enantioselective Magnesium Carbenoid 1,3-CH Insertion Reaction

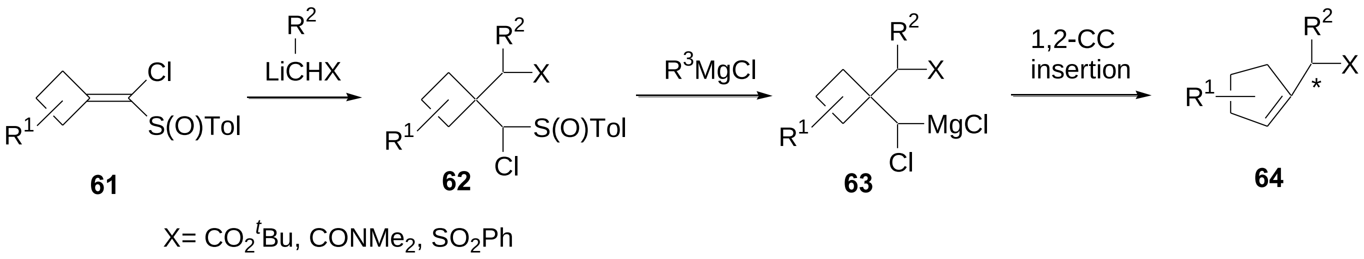
2-3. 1,2-CH Insertion and 1,2-Carbon Carbon (1,2-CC) Insertion Reaction

As described in section 2-2, magnesium carbenoids generated from 1-chloroalkyl *p*-tolyl sulfoxides (which were synthesized from ketones and carboxylic acid *tert*-butyl esters) gave cyclopropanes by the 1,3-CH insertion as the key reaction. In continuation of this chemistry, we investigated the property of magnesium carbenoid **50**, generated from 1-chloroalkyl *p*-tolyl sulfoxides **49**, which were derived from aldehydes via 1-chlorovinyl *p*-tolyl sulfoxide **48**, with a Grignard reagent (Scheme 7).[15,16] Contrary to our expectation, magnesium carbenoids **50** gave β,γ-unsaturated esters **51** or **52**, instead of the cyclopropanes, depending on the nature of the substituent R, in moderate to high yields. This procedure offers a novel method for a synthesis of β,γ-unsaturated esters from aldehydes.



Scheme 7. 1,2-CH and 1,2-CC Insertion Reaction of Magnesium Carbenoids Giving β,γ-Unsaturated Esters

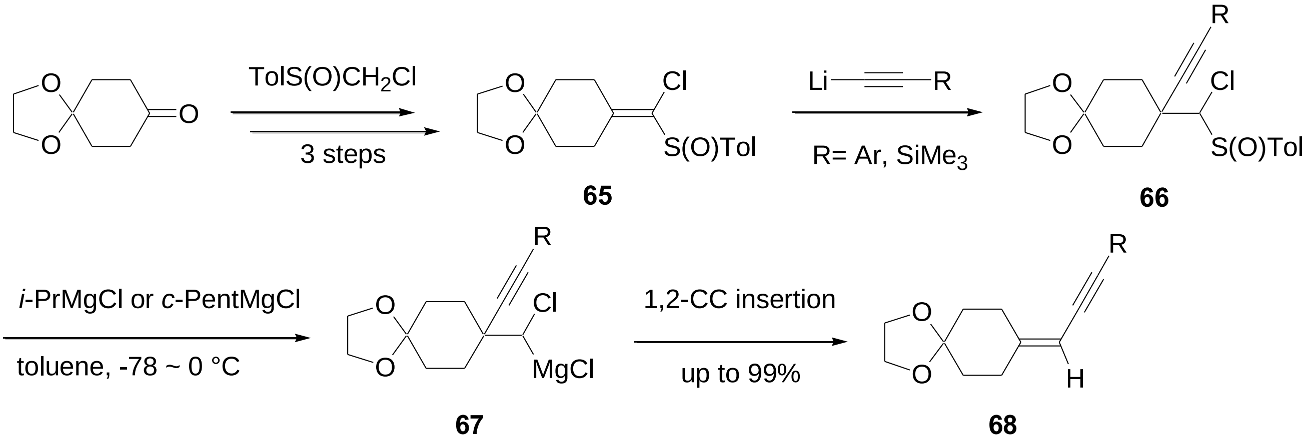
Thus, 1-chloroalkyl *p*-tolyl sulfoxide **54** derived from 3-phenylpropanal via **53** was treated with *i*-PrMgBr to afford β,γ-unsaturated ester **56** *via* 1,2-CH insertion of magnesium carbenoid intermediate **55** as the key reaction in up to 85% yield. In contrast to this, 1-chloroalkyl *p*-tolyl sulfoxide **58** derived from furfural and 2-formylthiophene via **57** was treated with EtMgCl to afford β,γ-unsaturated esters **59** or **60** via 1,2-CC insertion (rearrangement of aryl group) of magnesium carbenoid intermediates as the key reaction in up to 92% yield.[16]



Scheme 8. 1,2-CC Insertion Reaction of Magnesium Carbenoids **63** Derived from Cyclobutanones

In contrast to the 1,3-CH insertion reaction giving bicyclo[n.1.0]alkanes described in section 2-2 (Scheme 4 and 6), magnesium carbenoids **63** generated from **62** (which were synthesized from cyclobutanones through 1-chlorovinyl *p*-tolyl sulfoxides **61**) resulted in 1,2-CC insertion reaction to afford one-carbon ring-expanded cyclopentene derivatives in good to high yields (Scheme 8).[17] When enantiopure chloromethyl *p*-tolyl sulfoxide and carboxylic acid esters were used in this procedure, optically active cyclopentenes **64** were obtained in high *ee*.[18]

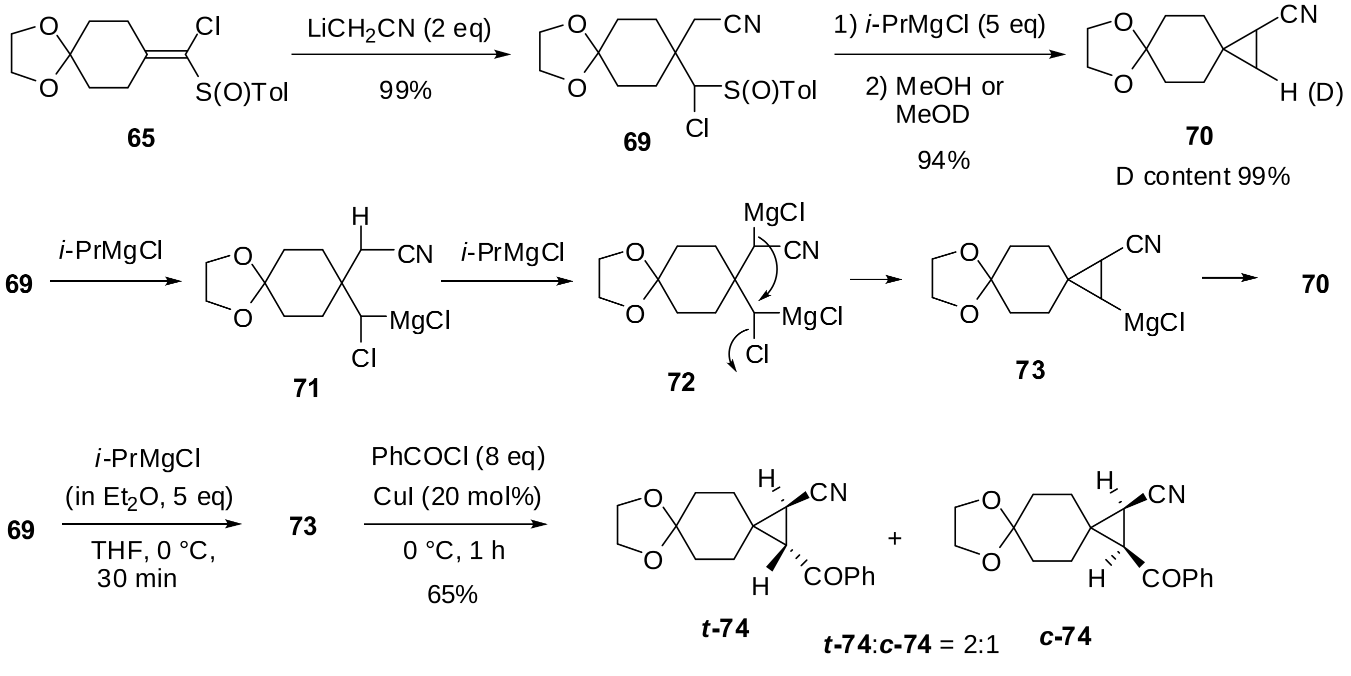
1,2-CC insertion reaction was observed in the reaction of magnesium carbenoids bearing an alkynyl group at the β-position (Scheme 9).[19,20] Thus, 1-chlorovinyl *p*-tolyl sulfoxide **65**, derived from 1,4-cyclohexanedione mono ethylene acetal, was treated with lithium acetylides to give adducts **66** in moderate to good yields. Treatment of this adducts with *i*-PrMgCl or cyclopentylmagnesium chloride resulted in the formation of conjugated enynes **68** in up to 99% yields by the 1,2-CC insertion reaction (migration of the acetylenic groups) of generated magnesium carbenoid intermediates **67**.



Scheme 9. 1,2-CC Insertion Reaction of Magnesium Carbenoids **67** Giving Conjugated Enynes **68**

2-4. S_N2-Type Reaction

Very interesting intramolecular S_N2 reaction of magnesium carbenoid was observed.[21] Thus, addition reaction of 1-chlorovinyl *p*-tolyl sulfoxide **65** with cyanomethyllithium afforded adduct **69**. Treatment of **69** with excess *i*-PrMgCl resulted in the formation of spiro-type cyanocyclopropane **70** in high yield. Quite interestingly, quenching of this reaction with CH_3OD afforded deuterated **70** with 99% deuterium incorporation. This result showed that this reaction is not the 1,3-CH insertion but S_N2 reaction (Scheme 10). The mechanism of this reaction is as follows. Treatment of **69** with *i*-PrMgCl results in the formation of magnesium carbenoid **71** by the sulfoxide-magnesium exchange reaction. The acidic hydrogen on the carbon bearing a cyano group was eliminated with the excess *i*-PrMgCl to produce cyano-stabilized carbanion **72**. Intramolecular S_N2 reaction of the magnesium carbenoid with the cyano-stabilized carbanion occurs to give cyclopropylmagnesium chloride intermediate bearing a cyano group **73**. Quenching of **73** with CH_3OD gives a cyanocyclopropane bearing deuterium at 2-position **70** (D) with high deuterium incorporation. Intermediate **73** was found to be able to be trapped with several electrophiles other than proton. The whole procedure becomes a new method for the synthesis of multi-substituted cyanocyclopropanes. Thus, after treatment of **69** with 5 equivalents of *i*-PrMgCl in THF at 0 °C, Cu(I) iodide (20 mol%) followed by benzoyl chloride (8 equiv) were added to the reaction mixture and the whole was stirred at 0 °C for 1 h. This procedure gave the desired benzoylated products **74** in 65% yield.

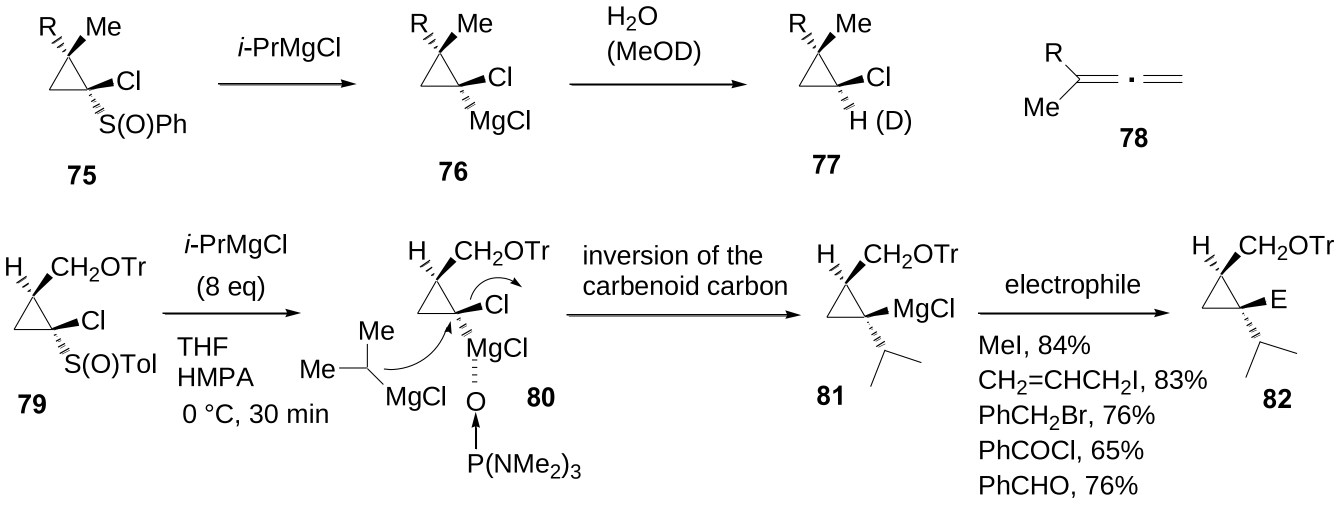


Scheme 10. Intramolecular S_N2 Reaction of Magneium Carbenoid **72** and Trapping of the Intermediate **73** with Benzoyl Chloride

3. CYCLOPROPYLMAGNESIUM CARBENOIDS

3-1. Alkylation of Cyclopropylmagnesium Carbenoids with a Grignard Reagnet

In 2001, the author's group reported for the first time the generation of cyclopropylmagnesium carbenoids **76** from 1-chlorocyclopropyl phenyl sulfoxides **75** with *i*-PrMgCl by the sulfoxide-magnesium exchange reaction at low temperature.[22] The generated magnesium carbenoids **76** were found to be stable at below -60 °C for at least 3 h. Quenching of this reaction with water or CH_3OD gave chlorocyclopropanes **77** in high yields. When this reaction was conducted at 0 °C, allenes **78** were obtained in high yield via the Doering-Moore-Skattebol reaction (Scheme 11).

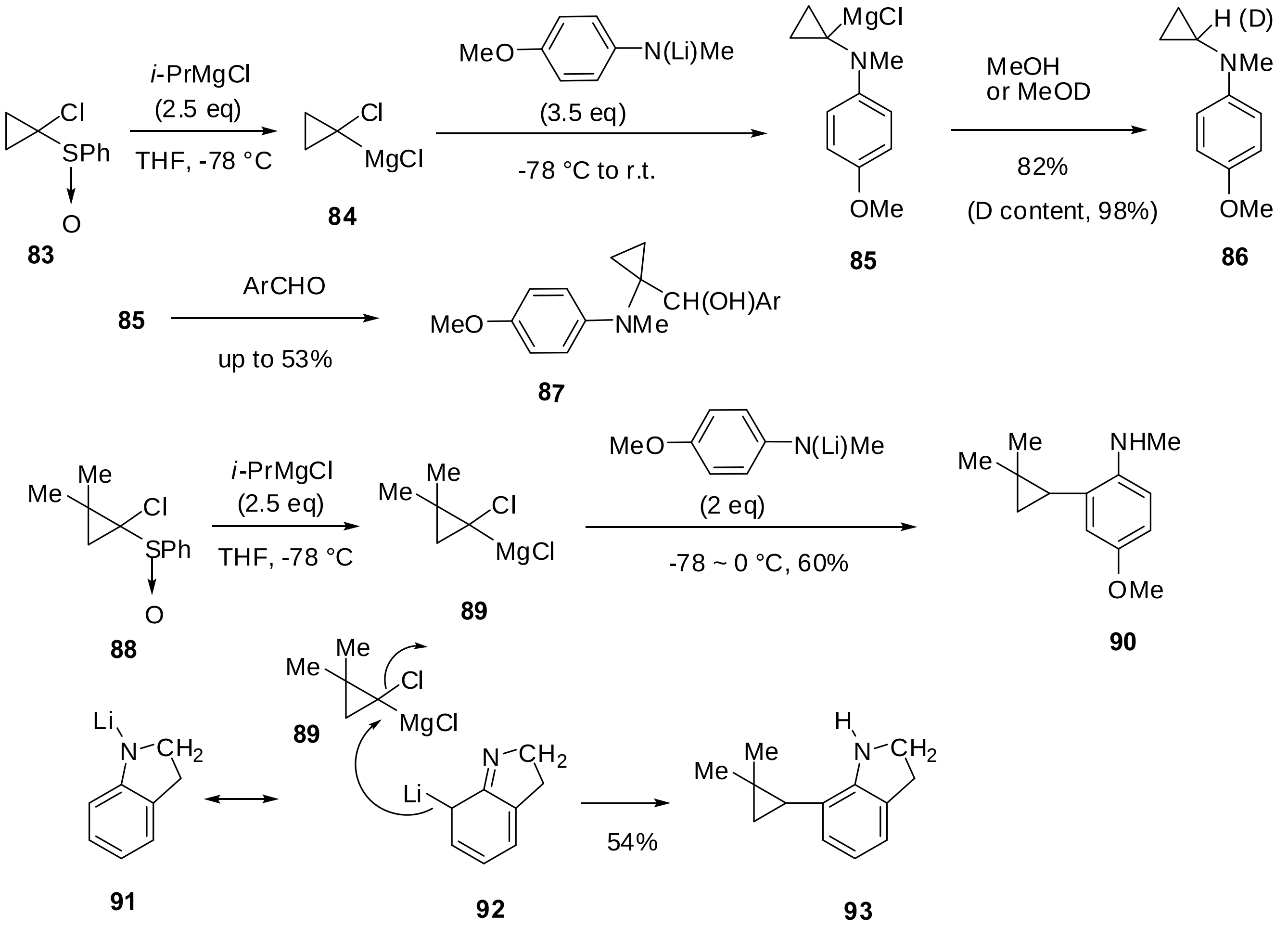


Scheme 11. Generation of Cyclopropylmagnesium Carbenoids from Aryl 1-Chlorocyclopropyl Sulfoxides and the Reaction with a Grignard Reagnet Followed by Electrophiles

Later, cyclopropylmagnesium carbenoids were found to be highly electrophilic.[23] Thus, 1-chlorocyclopropyl *p*-tolyl sulfoxide **79** was treated with excess *i*-PrMgCl in THF in the presence of HMPA gave alkylated cyclopropylmagnesium chloride **81** via cyclopropylmagnesium carbenoid **80** in good yield. The intermediate **81** was proved to be reactive with several electrophiles to give substituted cyclopropanes **82** in up to 84% yield. It is worth noting that above-mentioned alkylation is stereospecific reaction and two carbon-carbon bond-formations is carried out in one-pot to give multi-substituted cyclopropanes **82**.[23]

3-2. Reaction with *N*-Lithio Arylamines

The reactions of cyclopropylmagnesium carbenoids with *N*-lithio arylamines gave quite interesting results (Scheme 12).[24] Treatment of 1-chlorocyclopropyl phenyl sulfoxide **83** with *i*-PrMgCl resulted in the formation of cyclopropylmagnesium carbenoid **84**. To this reaction mixture, *N*-lithio *N*-methyl *p*-anisidine was added to give *N*-cyclopropylated alkyl magnesium chloride **85**. Quenching of this reaction with CH_3OD gave deuterated *N*-cyclopropylated *N*-methyl *p*-anisidine **86** in 82% yield with almost perfect deuterium incorporation. Quenching of this reaction with aryl aldehydes gave adduct **87** in up to 53% yield.

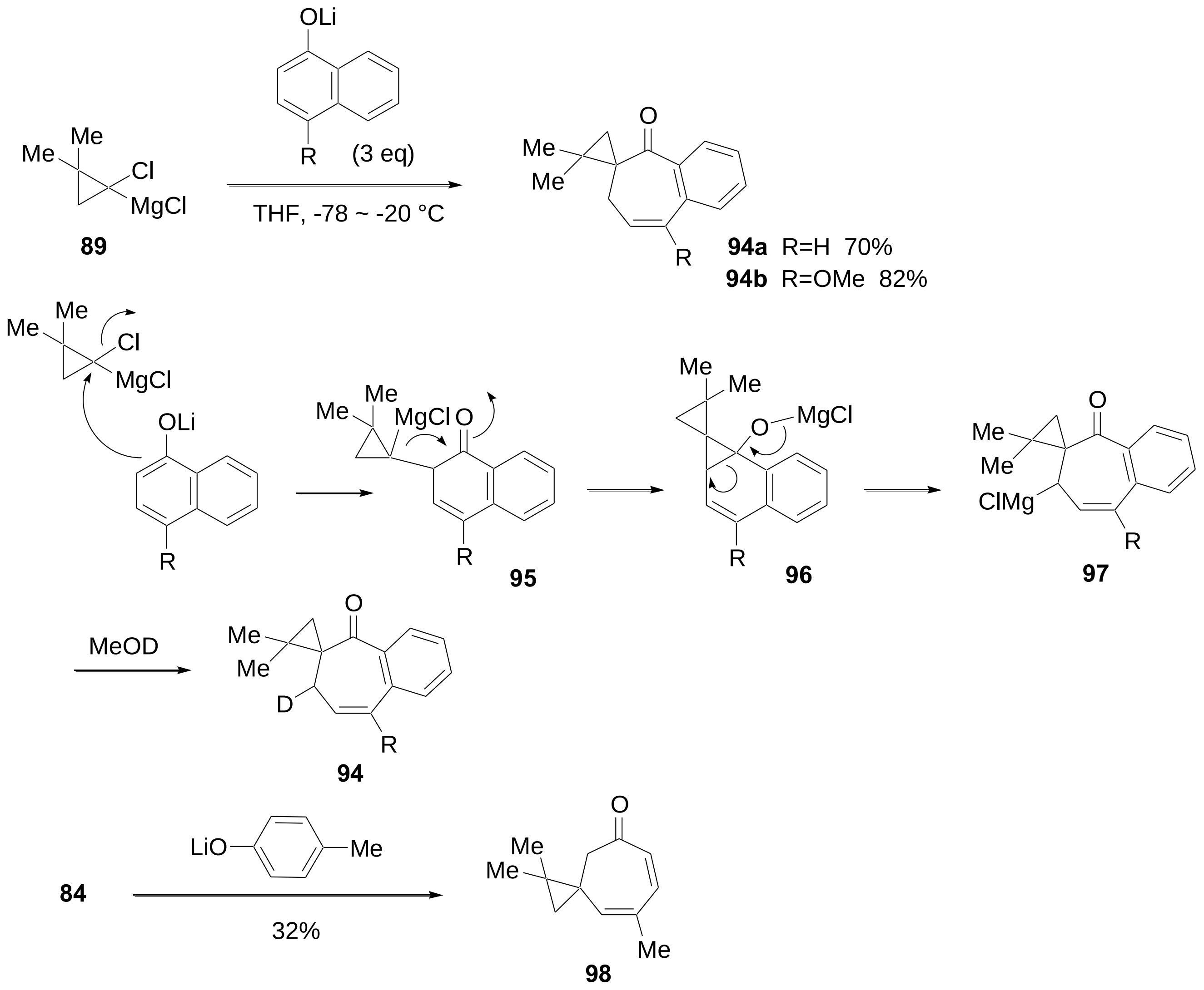


Scheme 12. *N*- and *C*-Cyclopropylation of *N*-Lithio Arylamines with Cyclopropylmagnesium Carbenoids

Very interestingly, treatment of cyclopropylmagnesium carbenoid **89**, generated from 1-chloro-2,2-dimethylcyclopropyl phenyl sulfoxide **88**, with *N*-lithio *N*-methyl *p*-anisidine gave *ortho*-cyclopropylated *N*-methyl *p*-anisidine **90** in 60% yield without *N*-cyclopropylated compound.[25] *N*-Lithio indoline **91** also reacted with **89** to give *ortho*-cyclopropylated product **93** without *N*-cyclopropylated compound via the reaction of **89** with resonance form **92**. In general, 1-chlorocyclopropyl phenyl sulfoxides bearing at least two substituents on the cyclopropane ring gave *ortho*-cyclopropylated products.[26]

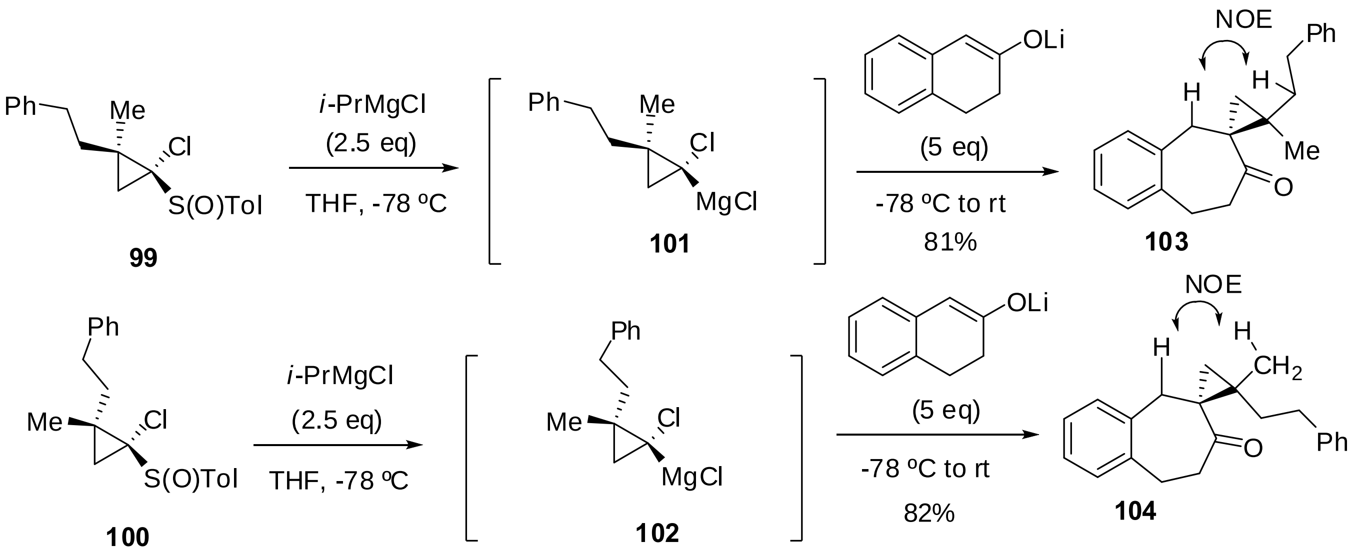
3-3. Reaction with *O*-Lithio Naphthols and Phenols

The reaction of cyclopropylmagnesium carbenoid **89** with *O*-lithio naphthols and phenols gave quite interesting one-carbon ring-expanded spiro[2.6]nonadienone derivatives **94** and **98** in variable yields (Scheme 13).[27]



Scheme 13. Reaction of *O*-Lithio 1-Naphthols and *O*-Lithio Phenols with Cyclopropylmagnesium Carbenoid **89** Giving Spiro[2.6]nonadienones **94** and **98**, and a Plausible Reaction Mechanism

Thus, treatment of cyclopropylmagnesium carbenoid **89** with 3 equiv of *O*-lithio 1-naphthols gave unexpected product, spiro[2.6]nonadienones **94** in up to 82% yield. A plausible mechanism of this reaction is as follows. Intermolecular S_N2 reaction of carbenoid carbon with α-carbon of naphtholate would afford cyclopropylmagnsium chloride intermediate **95**. Intramolecular alkylation of the carbanion to the carbonyl carbon would proceed to afford highly strained spiro[2.2]pentane intermediate **96**. Carbon-carbon bond-cleavage of the cyclopropanolate moiety, depicted in **96**, would take place easily because of the ring-strain to afford the final ring-expanded intermediate **97**. Protonolysis of **97** will give the product **94**. In order to confirm the final intermediate of this reaction to be **97**, deuteriolysis of this reaction with MeOD was carried out and indeed deuterated product **94** (D) was obtained with perfect deuterium incorporation. The reaction of **84** with *O*-lithio phenol gave similar product **98** with somewhat lower yield. The mechanism of this reaction must be different compared with that for the reaction of *O*-lithio naphthols.[27]

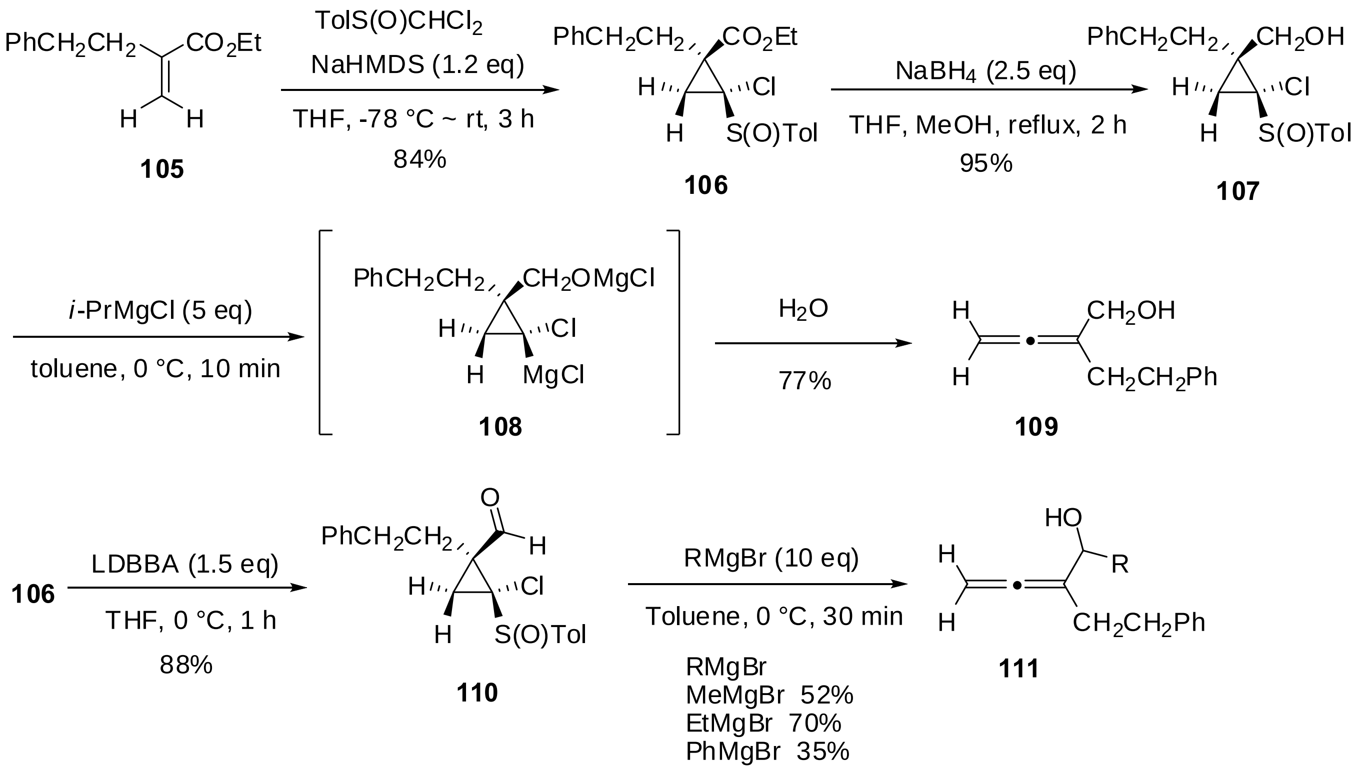


Scheme 14. The Stereospecific Reaction of Cyclopropylmagnesium Carbenoids **101** and **102**, Derived from 1-Chlorocyclopropyl *p*-Tolyl Sulfoxides **99** and **100**, Respectively, with Lithium Enolate of β-Tetralone

A similar reaction was found to be able to carry out with the lithium enolate of β-tetralone and the reaction was proved to be highly stereospecific (Scheme 14).[28] Thus, cyclopropylmagnesium carbenoids **101** and **102** were generated from sulfoxides **99** and **100**, respectively, with *i*-PrMgCl. Reaction of **101** with excess lithium enolate of β-tetralone gave one-carbon ring-expanded spiro[2.6]nonanone derivative **103** in 81% yield as a sole product. The same reaction of **102** gave **104** in 82% yield as a sole product. The products **103** and **104** are diastereomers to each other. Namely, these reactions are highly stereospecific. The mechanism and origin of this stereospecificity are described in the original paper.[28]

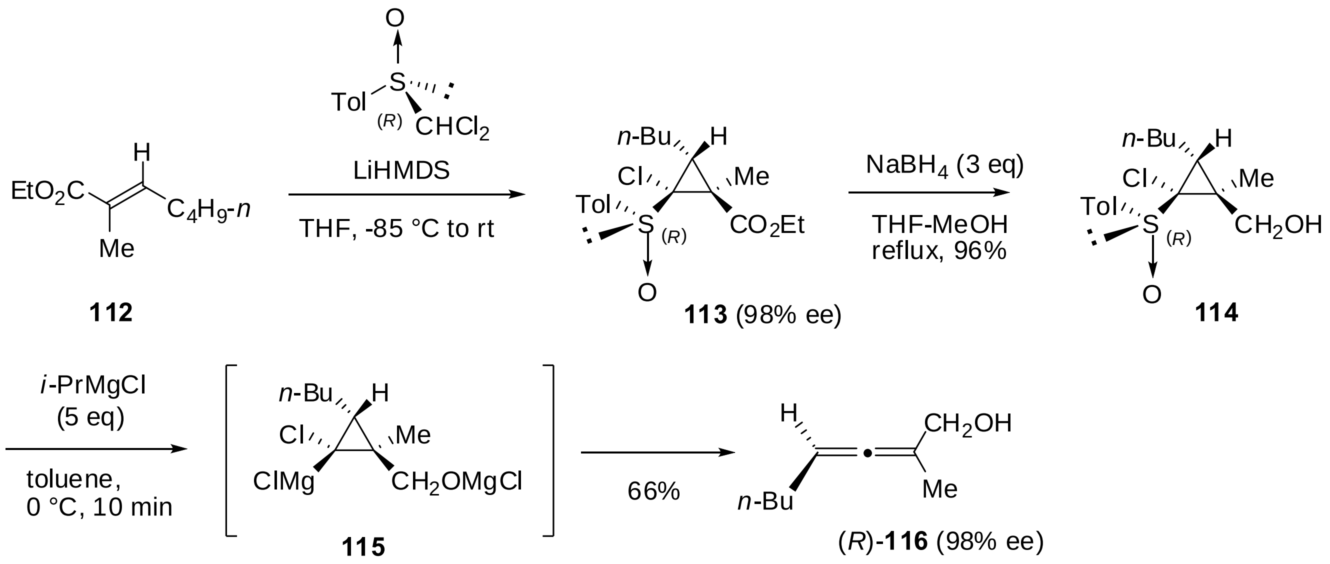
3-4. Doering-LaFlamme-type Rearrangement

As shown in Scheme 11, cyclopropyl carbenoids rearranged to allenes (Doering-LaFlamme allene synthesis) at around 0 °C. This reaction was applied to a short synthesis of α-allenic alcohols from α,β-unsaturated carbonyl compounds (Scheme 15).[29]



Scheme 15. Synthesis of α-Allenic Alcohols by the Doering-Moore-Skattebol Reaction of Cyclopropylmagnesium Carbenoid As the Key Reaction

Thus, treatment of α,β-unsaturated ester **105** with dichloromethyl *p*-tolyl sulfoxide in the presence of a base gave 1-chlorocyclopropyl *p*-tolyl sulfoxide **106** stereoselectively as a single product.[30] The ester group was reduced to a hydroxymethyl group to give **107** in quantitative yield. Finally, alcohol **107** was treated with excess *i*-PrMgCl in toluene at 0 °C to give α-allenic alcohol **109** via cyclopropylmagnesium carbenoid **108** in 77% yield. A short synthesis of secondary α-allenic alcohol **111** was also realized. Thus, adduct **106** was reduced directly to aldehyde **110** with lithium diisobutyl-*tert*-butoxyaluminum hydride (LDBBA) in good yield. Treatment of **110** with excess Grignard reagent resulted in the formation of secondary α-allenic alcohol **111** with nucleophilic addition of the Grignard reagent to the aldehyde and, at the same time, the sulfoxide-magnesium exchange reaction. It is worth noting that **111** was synthesized from **105** in only three steps in moderate overall yield.

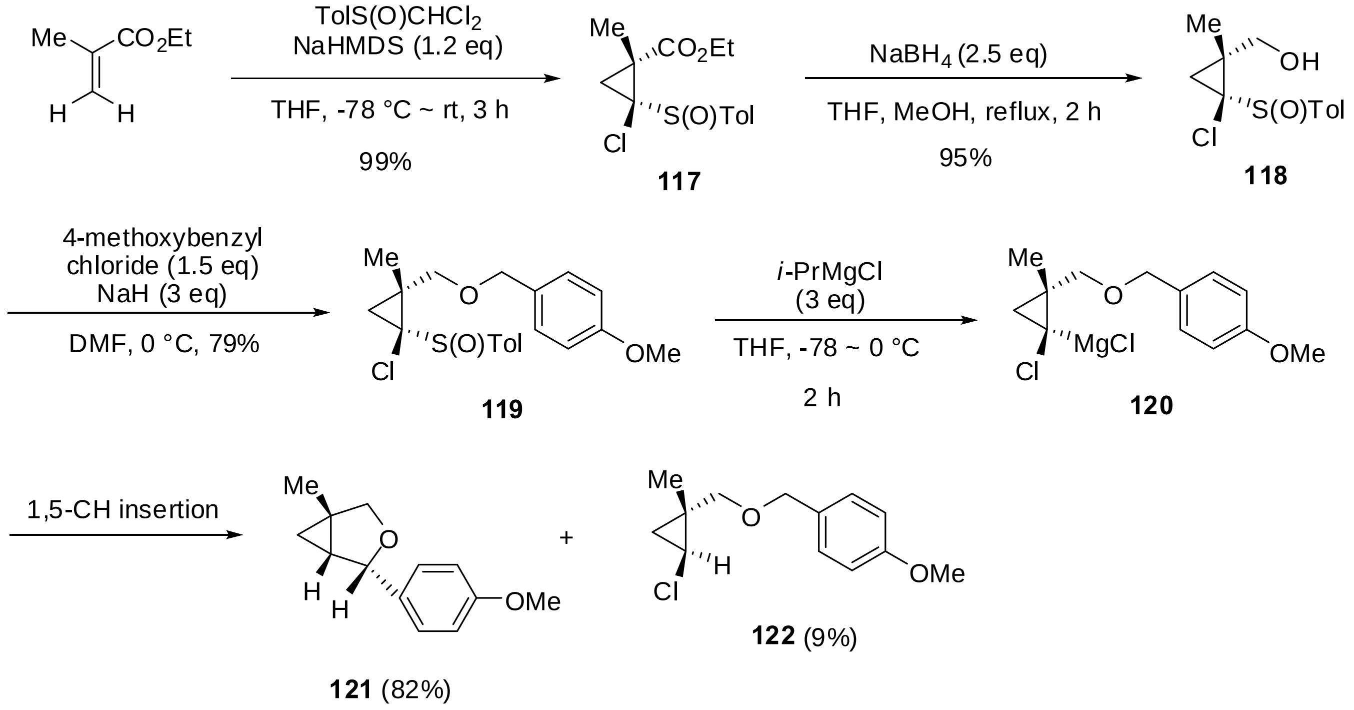


Scheme 16. Asymmetric Synthesis of Optically Active α-Allenic Alcohol (*R*)-**116** from α,β-Unsaturated Ester and (*R*)-Dichloromethyl *p*-Tolyl Sulfoxide by the Doering-LaFlamme Allene Synthesis

This procedure was extended to an asymmetric synthesis of α-allenic alcohols (Scheme 16).[31] The reaction of α,β-unsaturated ester **112** with enantiopure (*R*)-dichloromethyl *p*-tolyl sulfoxide[32] was carried out with LiHMDS to give cyclopropane **113** in high optical yield with moderate chemical yield. The ester group was reduced to a hydroxymethyl group to afford alcohol **114**. After the optical purity was improved to 99% by recrystallization, **114** was treated with *i*-PrMgCl to give optically active (*R*)-**116** via cyclopropylmagnesium carbenoid intermediate **115**. Absolute configuration, optical purity, and the mechanism of the asymmetric induction are described in the original paper.[31]

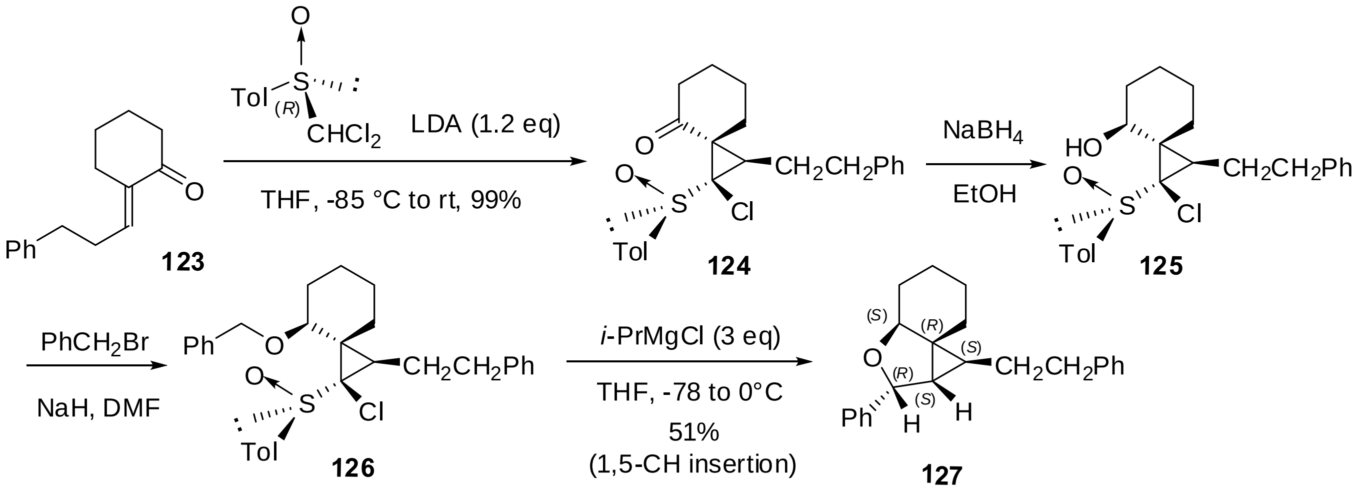
3-5. 1,5-CH Insertion Reaction

Cyclopropylmagnesium carbenoid generated from 1-chlorocyclopropyl *p*-tolyl sulfoxides bearing an alkoxymethyl group at the 2-position was found to take place 1,5-CH insertion reaction to give 3-oxabicyclo[3.1.0]hexanes in good yield (Scheme 17).[33] Treatment of ethyl methacrylate with dichloromethyl *p*-tolyl sulfoxide in the presence of NaHMDS gave cyclopropane **117** in quantitative yield. Reduction followed by alkylation of **117** gave 1-chlorocyclopropyl *p*-tolyl sulfoxides bearing an alkoxymethyl group at the 2-position **119** via alcohol **118**. Sulfoxide **119** was treated with *i*-PrMgCl to result in the generation of cyclopropylmagnesium carbenoid **120**. 1,5-CH insertion reaction of **120** proceeded to afford 3-oxabicyclo[3.1.0]hexane **121** in 82% yield along with protonated product **122**. This procedure offers a short synthesis of 3-oxabicyclo[3.1.0]hexanes from α,β-unsaturated carbonyl compounds with dichloromethyl *p*-tolyl sulfoxide in good overall yield.



Scheme 17. A Short Synthesis of 3-Oxabicyclo[3.1.0]hexane **121** from α,β-Unsaturated Ester by the 1,5-CH Insertion Reaction of Cyclopropylmagnesium Carbenoid **120** as the Key Reaction

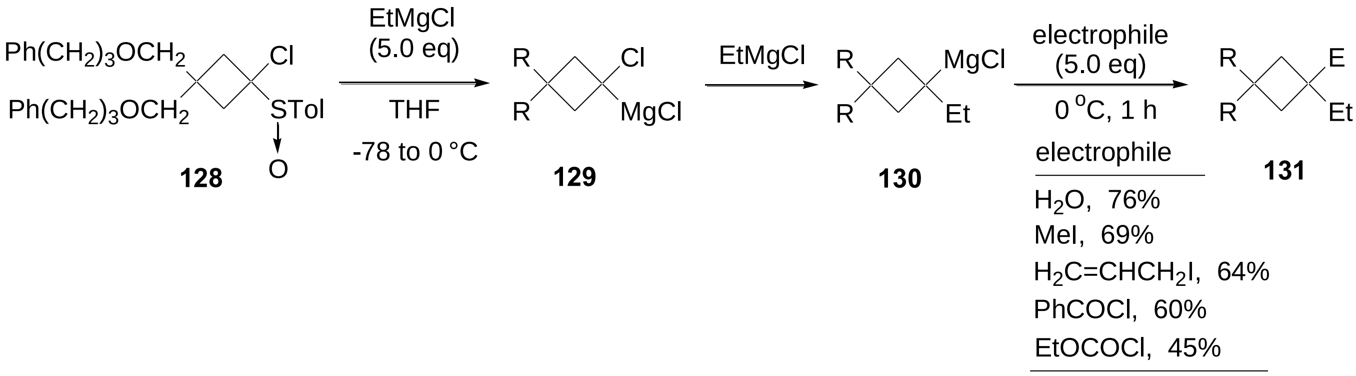
This procedure was applied to the asymmetric synthesis of 3-oxabicyclo[3.1.0]hexanes. As an example, asymmetric synthesis of 2-oxatricyclodecane **127** is described (Scheme 18).[34] Thus, treatment of α,β-unsaturated ketone **123** with (*R*)-dichloromethyl *p*-tolyl sulfoxid in the presence of LDA afforded enantiopure spiro-cyclopropane **124** in quantitative yield with perfect asymmetric induction from the sulfur chiral center. The ketone group was reduced and the resulting hydroxyl group was alkylated to give ether **126** in high overall yield via alcohol **125**. Absolute configuration of **125** was determined from X-ray analysis. Finally, **126** was treated with *i*-PrMgCl to give enantiopure (1*S*,3*R*,4*S*,5*S*,6*R*)-3-phenyl-5-(2-phenylethyl)-2-oxatricyclo[4.4.0.0^{4,6}]decane **127** in 51% yield through the 1,5-CH insertion reaction of the generated cyclopropylmagnesium carbenoid intermediate.[34]



Scheme 18. Asymmetric Synthesis of Oxatricyclodecane **127** from (*E*)-2-(3-Phenylpropylidene)-cyclohexanone **123**

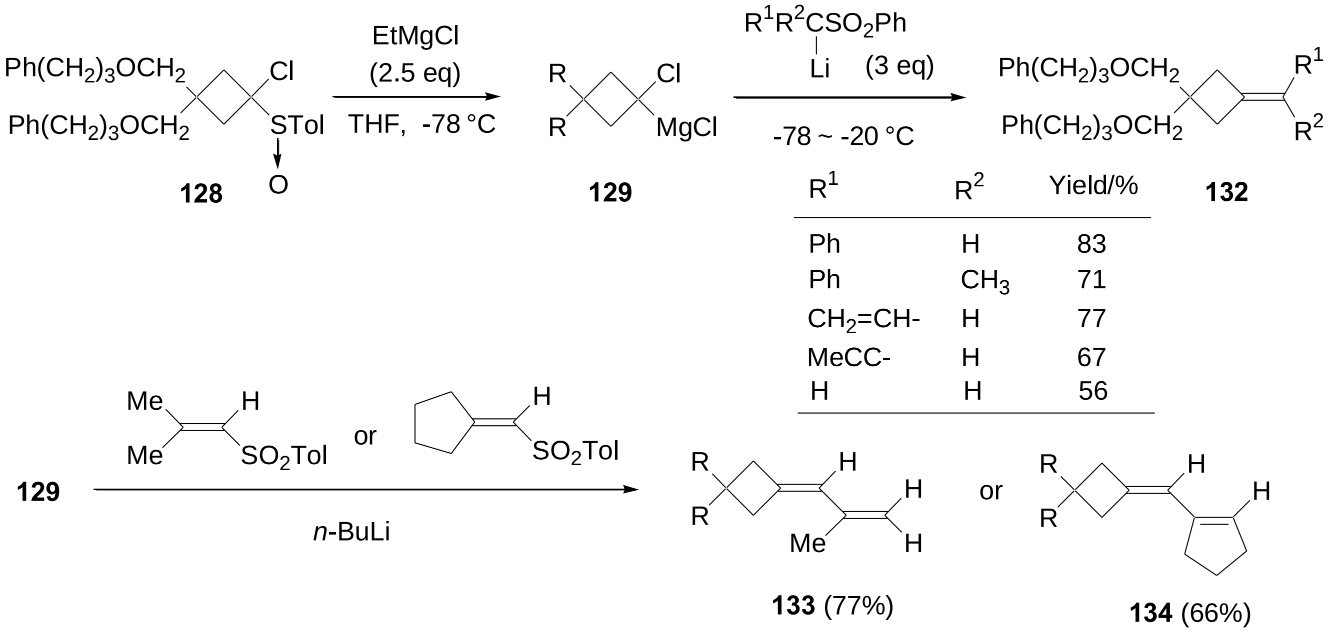
4. CYCLOBUTYLMAGNESIUM CARBENOID

4-1. Alkylation of Cyclobutylmagnesium Carbenoids with a Grignard Reagent



Scheme 19. Generation of Cyclobutylmagnesium Carbenoid **129** from 1-Chlorocyclobutyl *p*-Tolyl Sulfoxide **128** With a Grignard Reagent and Its Electrophilic Property

Similar to the cyclopropylmagnesium carbenoids described in chapter 3, cyclobutylmagnesium carbenoids, for example **129** in Scheme 19, can be generated from 1-chlorocyclobutyl *p*-tolyl sulfoxides with a variety of Grignard reagents at low temperature.[35] Cyclobutylmagnesium carbenoid **129** was proved to be stable at -78 °C for at least 30 min. When this reaction was conducted with excess Grignard reagent, for example EtMgCl, ethylated cyclobutylmagnesium chloride **130** was obtained. This result indicates that cyclobutylmagnesium carbenoids are quite electrophilic. Quenching of this intermediate **130** with several electrophiles, multi-substituted cyclobutanes **131** were obtained in moderate to good yield. It is noteworthy that multi-substituted cyclobutanes **131** were obtained from **128** in one-pot reaction with two carbon-carbon bond-formation.



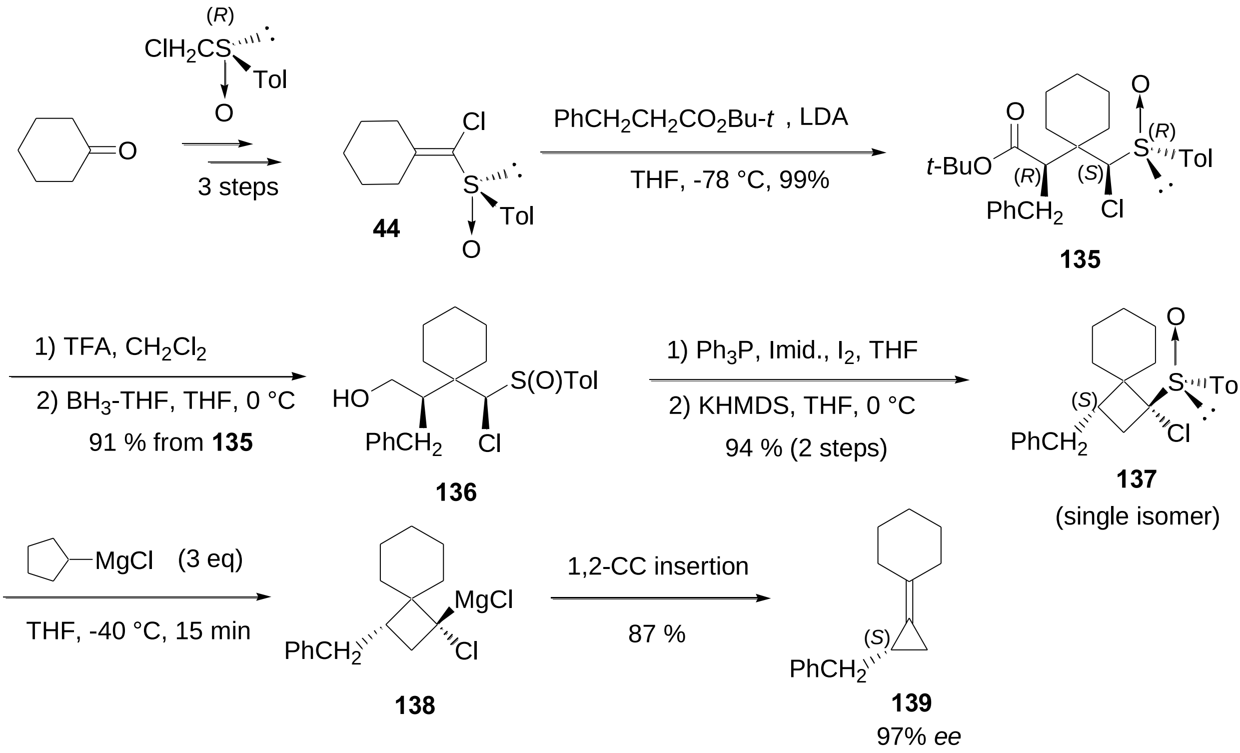
R^1	R^2	Yield/%
Ph	H	83
Ph	CH_3	71
CH_2=CH-	H	77
MeCC-	H	67
H	H	56

Scheme 20. Reaction of Cyclobutylmagnesium Carbenoid **129** with Lithiu α-Sulfonyl Carbanions to Give Alkylidene cyclobutanes **132** and Allylydenecyclobutanes **133** and **134**

A novel method for the synthesis of alkylidenecyclobutanes was realized by the reaction of cyclobutylmangesium carbenoids with lithium α-sulfonyl carbanions (Scheme 20).[36] For example, Treatment of 1-chlorocyclobutyl *p*-tolyl sulfoxide **128** with 2.5 equiv of EtMgCl in THF at -78 °C resulted in the formation of cyclobutylmagnesium carbenoid **129**. To this was added 3 equiv of lithium α-sulfonyl carbanion and the temperature of the reaction mixture was slowly allowed to warm to -20 °C to give alkylidenecyclobutanes **132** in up to 83% yield.[36] When this reaction was carried out with three equiv of lithium α-sulfonyl carbanions generated from vinyl sulfones (for example, the vinyl sulfones shown in Scheme 20) with *n*-BuLi, allylidenecyclobutanes **133** or **134** were obtained in good yields. Actual reactive species of this reaction was proved to be lithium α-sulfonyl carbanion of allyl sulfones.[37]

4-3. 1,2-CC Insertion Reaction Giving Alkylidenecyclopropanes

Very interesting 1,2-CC insertion reaction of cyclobutylmagnesium carbenoid giving alkylidenecyclopropanes was found and this reaction was applied to the synthesis of enatniopure alkylidenecyclopropanes (Scheme 21).[38] Thus, optically active 1-chlorovinyl *p*-tolyl sulfoxide **44** was treated with lithium enolate of *tert*-butyl 3-phenylpropionate to afford adduct **135** in quantitative yield.



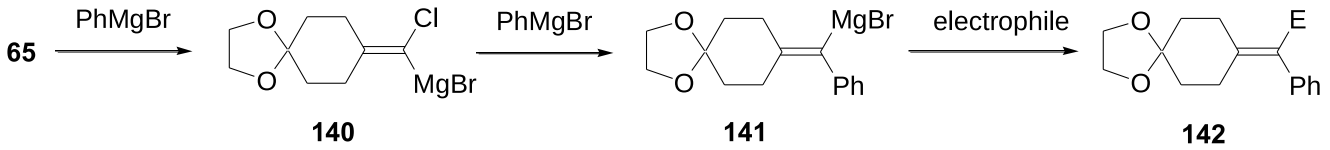
Scheme 21. A New Asymmetric Synthesis of Alkylidenecyclopropanes by 1,2-CC Insertion of Cyclobutylmagnesium Carbenoids as the Key Reaction

Stereochemistry of the adduct **135** (*syn*-relationship between the chlorine atom and the benzyl group) was determined based on our previous study. The adduct was treated with trifluoroacetic acid in dichloromethane to give a carboxylic acid, which was reduced with BH_3-THF in THF at 0 °C to give alcohol **136** in 91% overall yield from **135**. The hydroxyl group in **136** was converted to iodide group under the conventional reaction and the resultant iodide was treated with two equivalents of KHMDS to give the desired 1-chlorocyclobutyl *p*-tolyl sulfoxide **137** in 94% overall yield from **136** as a single product. The key reaction was carried out with cyclopentylmagnesium chloride at -40 °C to give optically active alkylidenecyclopropane **139** in 87% yield with 97% ee via the 1,2-CC insertion reaction of cyclobutylmagnesium carbenoid intermediate **138**.[38]

5. MAGNESIUM ALKYLIDENE CARBENOIDS

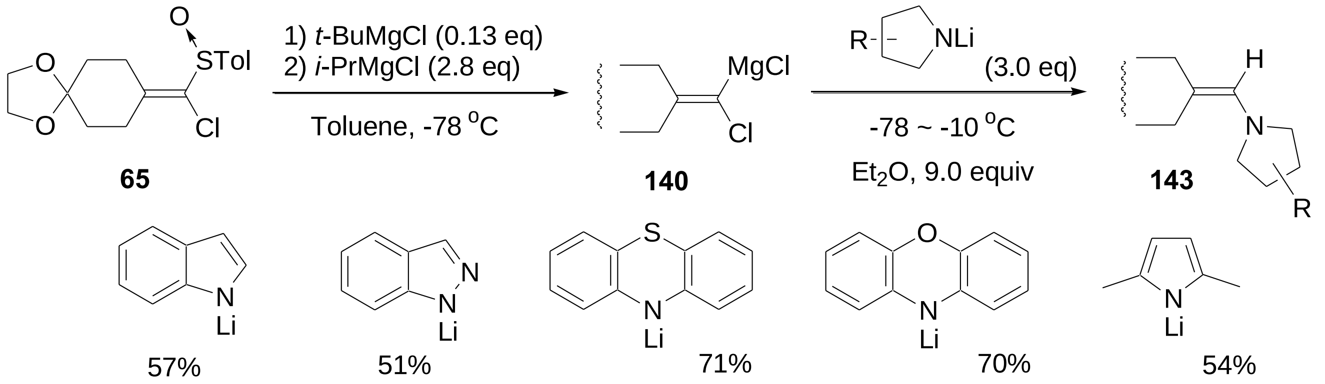
5-1. Reaction of Magnesium Alkylidene Carbenoids with Nitrogen-containing Heterocycles

Previously, the author’s group reported, for the first time, the generation of magnesium alkylidene carbenoids **140** from 1-chlorovinyl *p*-tolyl sulfoxide **65** with a Grignard reagent. The magnesium alkylidene carbenoids were found to be quite electrophilic (Scheme 22).[39] For example, treatment of **65** with excess phenylmagnesium bromide at low temperature resulted in the formation of magnesium alkylidene carbenoid **140**, which reacted with the used phenylmagnesium bromide electrophilically to afford phenylated alkenylmagnesium bromide intermediate **141**. The intermediate **141** was proved to be reactive with a variety of electrophiles to afford tetra-substituted olefin **142** in moderate to good yields with continuous two carbon-carbon bond-formation in one-pot. Later, magnesium alkyliene carbenoid **140** was found to be stable at -78 °C for at least 30 min.[40]



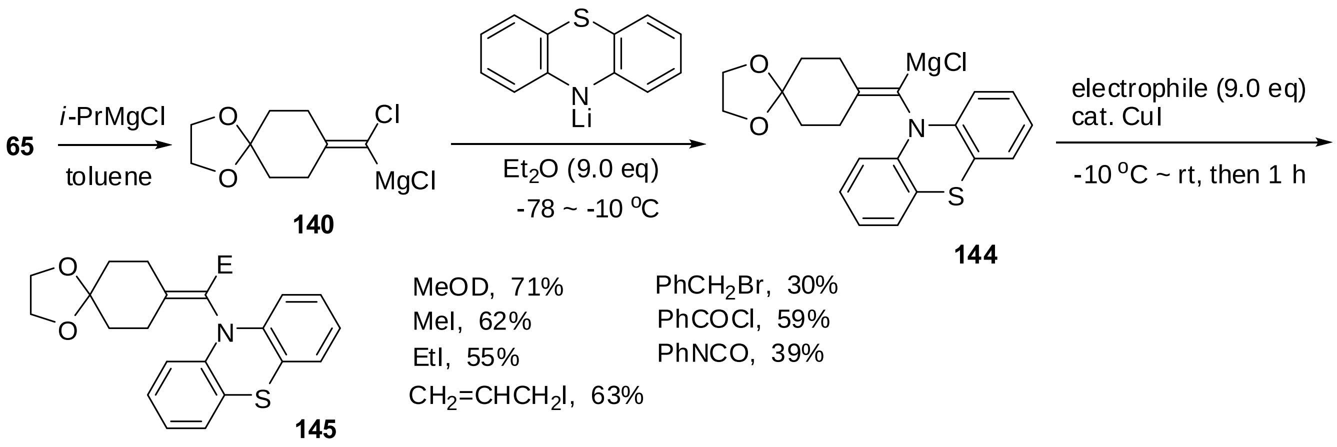
Scheme 22. Generation of Magnesium Alkylidene Carbenoid **140** from 1-Chlorovinyl *p*-Tolyl Sulfoxide **65** With a Grignard Reagnet and its Electrophilic Nature

As described above, magnesium alkylidene carbenoids were proved to be quite electrophilic. We found that the reaction of carbenoid **140** with *N*-lithio nitrogen-containing heterocycles gave *N*-alkenylated nitrogen-containing heterocycles **143** (Scheme 23).[41] For example, treatment of **65** in toluene with *i*-PrMgCl followed by *N*-lithio indole afforded *N*-alkenylindole **143** in 57% yield. The reaction with *N*-lithio phenothiazine and phenoxazine gave better yields of 70%. This reaction provides unique way for the direct *N*-alkenylation of nitrogen-containing heterocycles.



Scheme 23. Direct *N*-Alkenylation of Nitrogen-containing Heterocycles with Magnesium Alkylidene Carbenoid **140**

The intermediate of this reaction was proved to be alkenylmagnesium compounds, which could be trapped with several electrophiles to give nitrogen-containing heterocycles bearing a fully substituted olefin on the nitrogen (Scheme 24).[41]

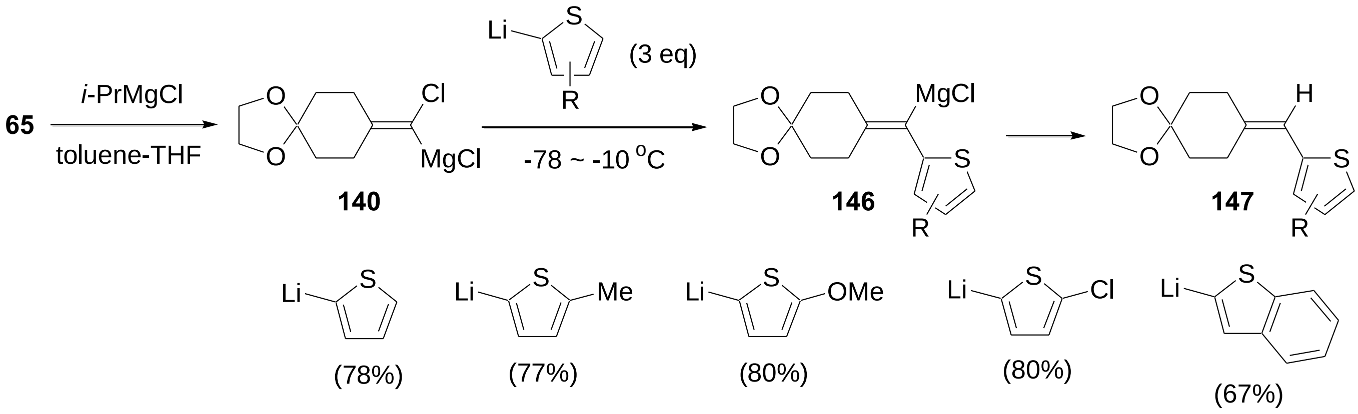


Scheme 24. Reaction of Magnesium Alkylidene Carbenoid **140** with *N*-Lithio Phenothiazine Followed by Several Electrophiles Giving Olefins **145** Bearing Phenothiazine and Electrophiles

Thus, reaction of **65** with *i*-PrMgCl gave magnesium alkylidene carbenoid **140**. To this reaction mixture was added three equiv of *N*-lithio phenothiazine and temperature of the reaction mixture was slowly allowed to warm to -10 °C to give alkenylmagnesium intermediate **144**. Finally, excess electrophile was added to the reaction mixture to give phenothiazine bearing a fully substituted olefin **145** in moderate yield in one-pot reaction.[41]

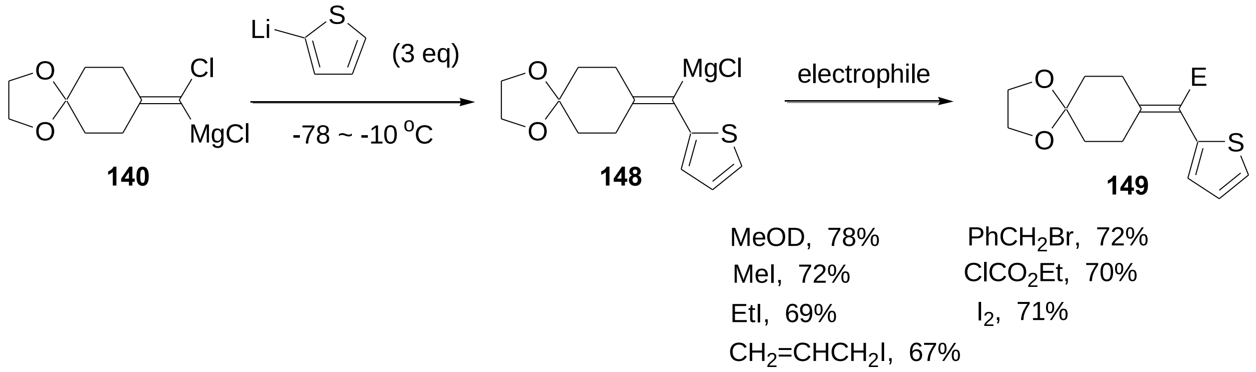
5-2. Reaction of Magnesium Alkylidene Carbenoids with Thiophenes and Furans

Magnesium alkylidene carbenoids were found to be reactive with 2-lithiothiophenes in good yields (Scheme 25).[42] Thus, treatment of magnesium alkylidene carbenoid **140**, derived from **65** with *i*-PrMgCl in a mixture of toluene-THF, with three equiv of 2-lithiothiophene afforded 2-alkenylthiophene **147** (R=H) in 78% yield via alkenylmagnesium chloride intermediate **146**. As shown in Scheme 25, various kinds of 2-lithiothiophenes reacted with **140** to give 2-alkenylthiophenes **147** in good yields.

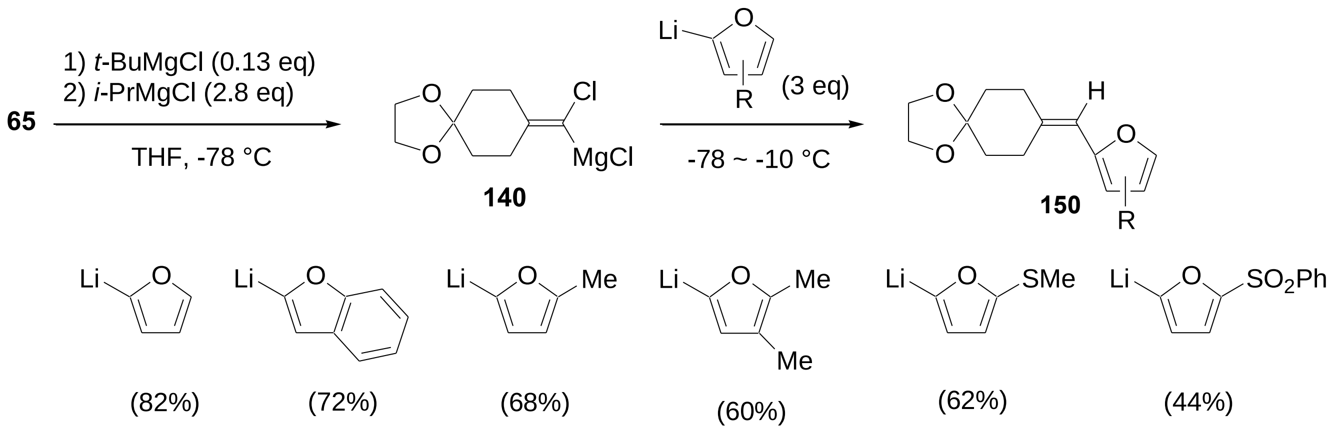


Scheme 25. Reaction of Magnesium Alkylidene Carbenoid **140** with 2-Lithiothiophenes Giving 2-Alkenylthiophenes **147**

The alkenylmagnesium chloride intermediates **146** were proved to be reactive with several electrophiles to give thiophenes bearing a fully substituted olefin at the 2-position in good yields. Representative examples are shown in Scheme 26.[42] Thus, the reaction of magnesium alkylidene carbenoids **140** with 2-lithiothiophene gave alkenylmagnesium chloride intermediate **148**. To this reaction mixture was added excess amount of electrophiles to give thiophenes bearing a fully substituted olefin **149** in up to 72% yield. This reaction provides a unique way for the synthesis of thiophenes having a fully substituted olefin at the 2-position in relatively short steps.

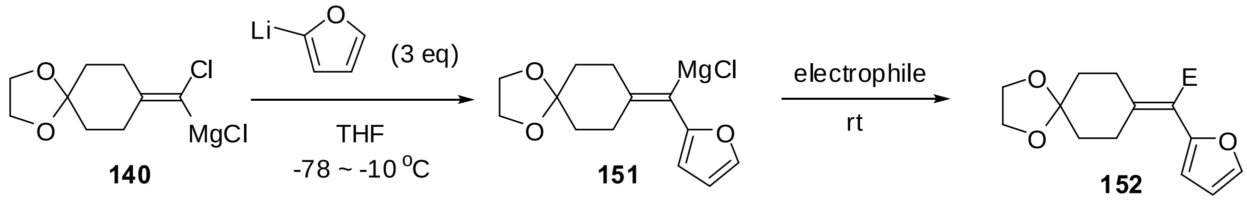


Scheme 26. Reaction of Magnesium Alkylidene Carbenoid **140** with 2-Lithiothiophene Followed by Several Electrophiles Giving Thiophene Bearing a Fully Substituted Olefin **149**



Scheme 27. Reaction of Magnesium Alkylidene Carbenoid **140** with 2-Lithiothiofurans Followed by Several Electrophiles Giving Furans Bearing a Fully Substituted Olefin **150**

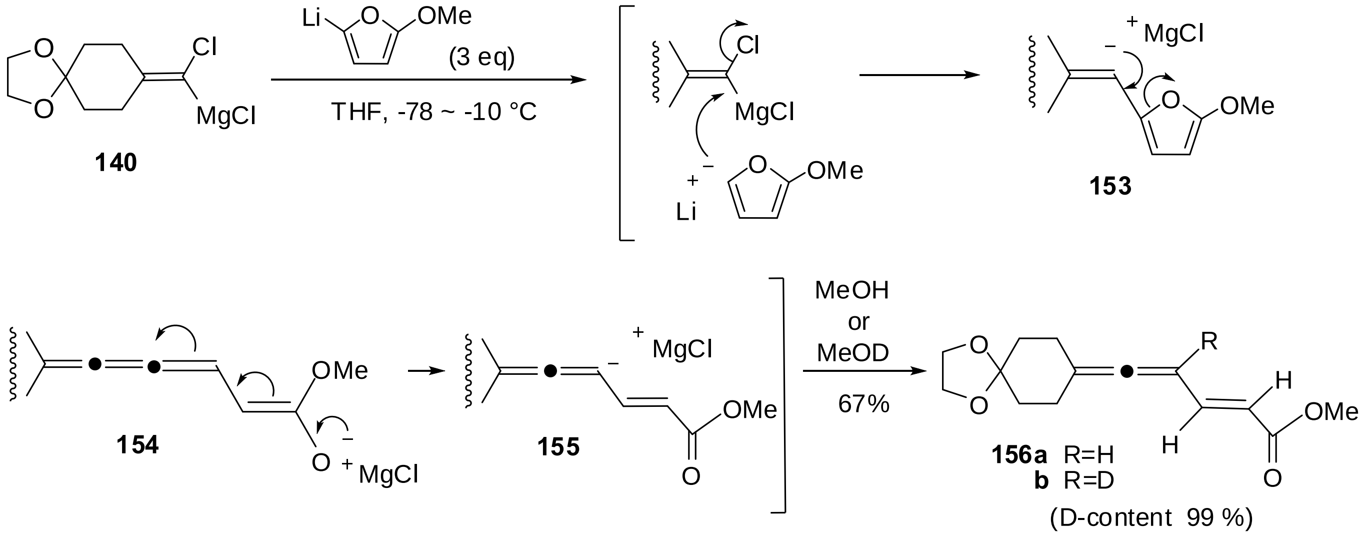
A similar reaction can be conducted with 2-lithiofurans (Scheme 27).[43] Thus, 1-chlorovinyl *p*-tolyl sulfoxide **65** was treated with *t*-BuMgCl followed by *i*-PrMgCl in THF at -78 °C to give magnesium alkylidene carbenoid **140**. A solution of 2-lithiofuran (generated from furan with *n*-BuLi in THF; 3 equivalents) was added to the solution of **140** and the temperature of the reaction mixture was slowly allowed to warm to -10 °C. This reaction gave the desired 2-alkenylfuran **150** (R=H) in 82% yield. The results for the reaction of **140** with various kinds of 2-lithiofurans to give 2-alkenylfurans are summarized in Scheme 27.



MeOD, 78%
MeI, 79%
EtI, 67%
$CH_2=CHCH_2I$, 75%
$PhCH_2Br$, 73%
$ClCO_2Et$, 62%
I_2, 70%
PhCHO, 73%

Scheme 28. Reaction of Magnesium Alkylidene Carbenoid **140** with 2-Lithiofuran Followed by Several Electrophiles Giving Furans Bearing a Fully Substituted Olefin **152**

The intermediate of this reaction was again found to be the alkenylmagnesium **151** (Schene 28). Thus, quenching the reaction of **140** with 2-lithiofuran with MeOD gave deuterated alkenylfuran **152** (E=D) in 78% yield with 96% deuterium content. In the same way described above, the intermediate **151** could be trapped with various electrophiles to afford furans bearing a fully substituted alkene at the 2-position **152** in good yields.

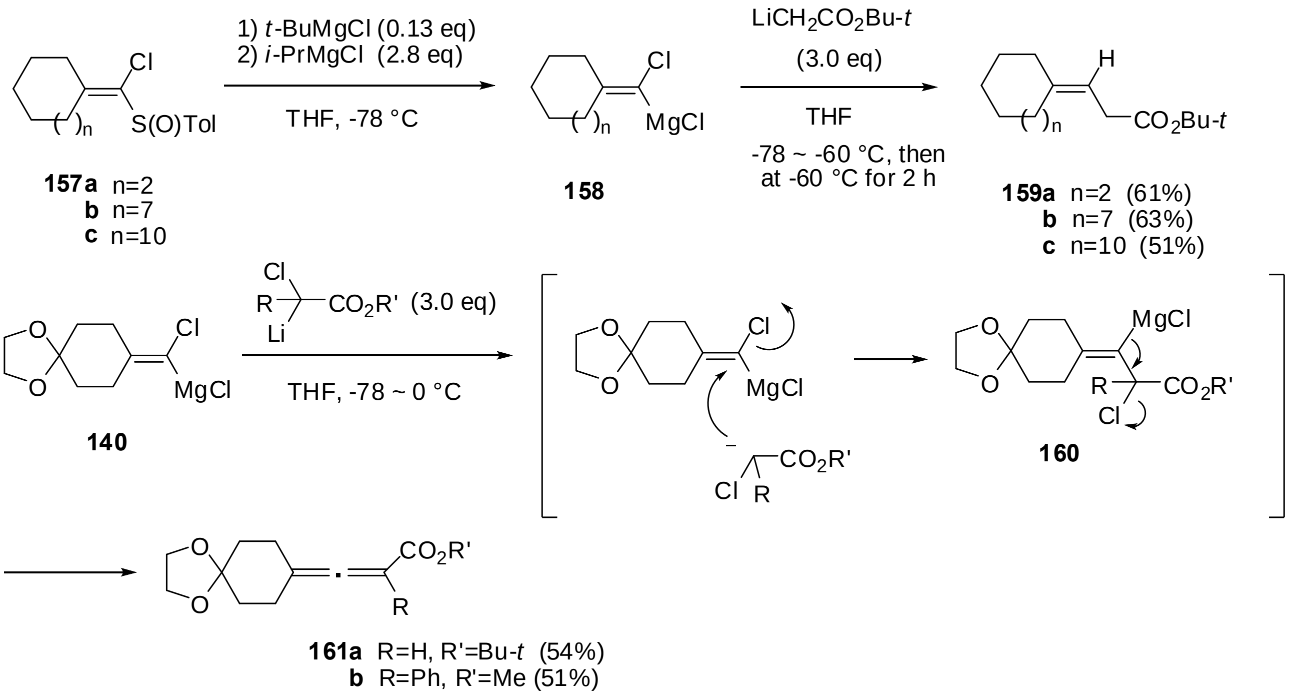


Scheme 29. Allene Conjugated with α,β-Unsaturated Methyl Ester **156** by the Reaction of Magnesium Alkylidene Carbenoid **140** with 2-Lithio-5-methoxyfuran

Very interesting reaction was found from the reaction of magnesium alkylidene carbenoid **140** with 2-lithio-5-methoxyfuran (Scheme 29).[43] Reaction of **140** with 2-lithio-5-methoxyfuran under the same conditions as described above gave an unexpected product **156a** in 67% yield. From the spectral data, an allene conjugated with α,β-unsaturated methyl ester was determined to be the structure of the product **156a**. A plausible mechanism for the reaction is shown in Scheme 29. Thus, 2-lithio-5-methoxyfuran attacks the carbenoid carbon to give alkenylmagnesium intermediate **153**. The anion would cleave the C-O bond of the furan ring to afford 1,2,3-triene conjugated with enolate **154**. This triene intermediate must be unstable and transfer of the charge on the oxygen to the allenic carbon gives intermediate **155**, which is protonated to give product **156a**. When this reaction was quenched with MeOD, deuterated allene **156b** was obtained with perfect deuterium incorporation.

5-3. Reaction of Magnesium Alkylidene Carbenoids with Lithium Ester Enolates

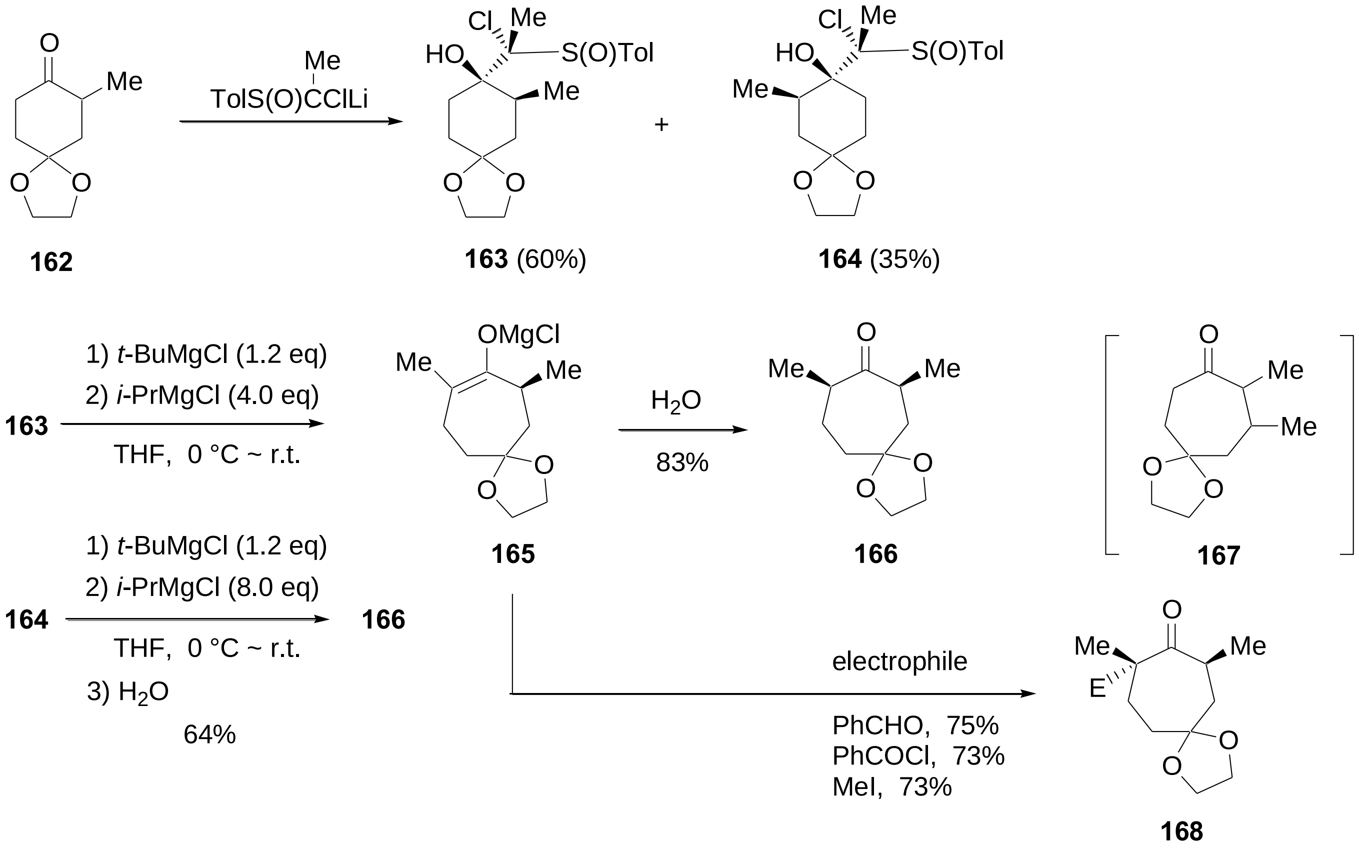
Magnesium alkylidene carbenoids were found to be reactive with lithium ester enolates to afford β,γ-unsaturated esters in moderate yields (Scheme 30).[44] Thus, the treatment of magnesium alkylidene carbenoids **158** derived from 1-chlorovinyl *p*-tolyl sulfoxides **157** with lithium enolate of *tert*-butyl acetate gave β,γ-unsaturated esters **159** in up to 63% yield. Although the yields are not always good at the present, this method is an unprecedented way and contributes to a synthesis of various β,γ-unsaturated esters. When lithium ester enolate of *tert*-butyl chloroacetates were used in this reaction, allenic esters **161** were obtained in up to 54% yield. Thus, treatment of magnesium alkylidene carbenoid **140** with lithium enolate of *tert*-butyl chloroacetate under the conditions shown in Scheme 30 gave allenic ester **161a** in 54% yield. This reaction is presumed to proceed as follows. The lithium ester enolate attacks the carbenoid carbon of **140** to give alkenylmagnesium intermediate **160** with inversion of the configuration of the carbenoid carbon. β-Elimination of both the magnesium chloride and the chlorine atom in intermediate **160** took place simultaneously to afford allenic ester **161**.



Scheme 30. Reaction of Magnesium Alkylidene Carbenoids with Various Lithium Ester Enolates

6. MAGNESIUM β-OXIDO CARBENOIDS

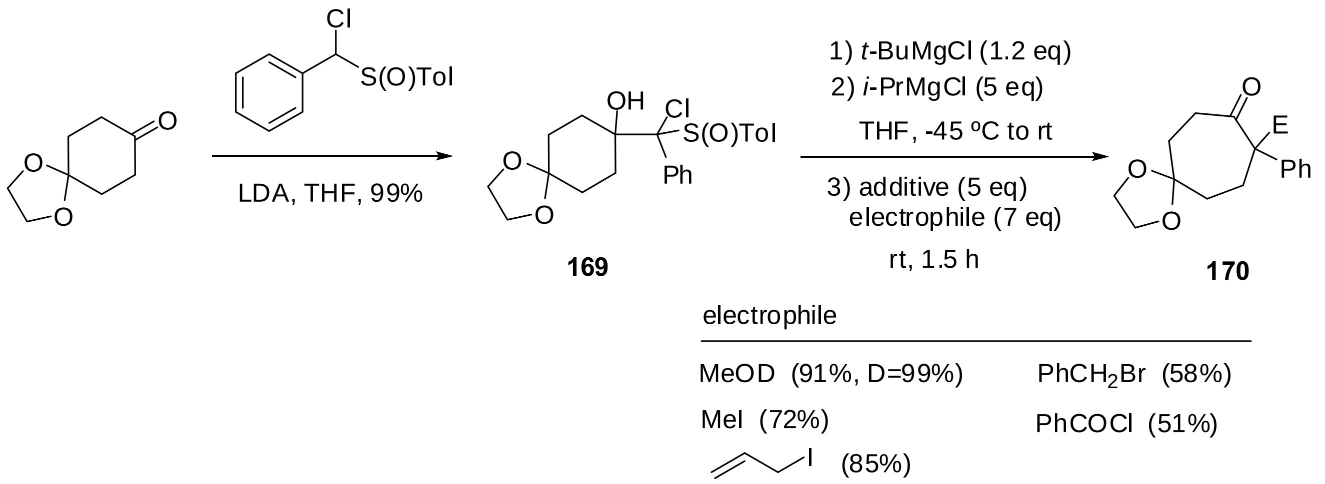
β-Oxido carbenoid rearrangement is one of the most useful reactions for the homologation and/or elongation of carbonyl compounds. Several methods for the homologation of carbonyl compounds by using the β-oxido carbenoid rearrangement as the key reaction have been reported.[45] We recently reported an interesting one-carbon homologation of ketones by using the magnesium β-oxido carbenoid rearrangement as the key reaction (Scheme 31).[46] Thus, the reaction of the lithium α-sulfinyl carbanion of 1-chloroethyl *p*-tolyl sulfoxide with cyclohexanone derivative **162** gave two adducts **163** (60%) and **164** (35%) as easily separable two diastereomers. The stereochemistry of each adduct was determined by X-ray crystallographic analysis. Main adduct **163** was treated with *t*-BuMgCl (1.2 equiv) followed by *i*-PrMgCl (4 equiv) in THF at 0 °C. The sulfoxide-magnesium exchange reaction took place smoothly to give ring-expanded product **166** in 83% yield with trace amount of isomer **167**. Significant difference in the reactivity of **163** and **164** with *i*-PrMgCl was observed. Thus, when the minor adduct **164** was treated with *t*-BuMgCl (1.2 equiv) followed by *i*-PrMgCl (4 equiv) in THF, the reaction was rather slow and significant amount of starting material **164** was recovered. Increasing of the amount of *i*-PrMgCl (8



Scheme 31. One-carbon Ring-expansion of Unsymmetrical Cylclohexanone **162** to 2,7-Disubstituted Cyclohepanone **166** and Trapping the Magnesium Enolate Intermediate **165** Giving 2,2,7-Trisubstituted Cycloheptanones **168**

equiv) and prolonging the reaction time gave completed reaction and the same cycloheptanone **166** was obtained in 64% yield. Namely, these two reactions are highly selective. The rational explanation of this selectivity and the difference of the reactivity are described in the original paper.[47] The intermediate of this β-oxido carbenoid rearrangement was proved to be magnesium enolate **165**, which could be trapped with electrophiles to give 2,2,7-trisubstituted cycloheptanones **168** in good yields from **163** in one-pot.[47]

In continuation of the study for one-carbon homologation of carbonyl compounds using β-oxido carbenoid rearrangement as the key reaction, we recently investigated the synthesis of aryl(chloro)methyl *p*-tolyl sulfoxides and uses them in the synthesis of α-aryl ketones (Scheme 32).[48] A representative example is shown in Scheme 32. Thus, the addition reaction of lithium α-sulfinyl carbanion derived from chloro(phenyl)methyl *p*-tolyl sulfoxide with cyclohexanone derivative gave adduct **169** in quantitative yield. Sequential treatment of **169** with *tert*-BuMgCl and *i*-PrMgCl resulted in the one-carbon ring-expanded magnesium enolate intermediate via the magnesium β-oxido carbenoid. Finally, trapping of this intermediate with various electrophiles afforded 9-substituted-9-phenyl-2,4-dioxaspiro[4.6]undecane-8-one **170** in up to 85% yield from adduct **169**. Although there are some limitations in this procedure, our results contribute to the synthesis of α-aryl ketones from aldehydes and ketones by one-carbon homologation and/or elongation.



Scheme 32. Synthesis of 9-Substituted 9-Phenyl-2,4-dioxaspiro[4.6]undecane-8-ones **170** from 1,4-Cyclohexanedione Mono Ethylene Acetal and Chloro(phenyl)methyl *p*-Tolyl Sulfoxide

7. CONCLUSION

As magnesium carbenoids, outlined in this review, are relatively stable compared with the corresponding traditional lithium carbenoids, we can manage the magnesium carbenoids in a similar way as the usual reactants with a little precaution. Concerning the generation of the magnesium carbenoids, starting from sulfoxides bearing chlorine atom on the α-position with Grignard reagents via the sulfoxide-magnesium exchange reaction gives much higher versatility compared with the halogen-magnesium exchange reaction. The magnesium carbenoids show both nucleophilic and electrophilic properties; however, the electrophilic reaction with nucleophiles is far more interesting from the synthetic viewpoint. Many new and very interesting results will be forthcoming from this field.

REFERENCES AND NOTES

1. Some monographs and reviews concerning chemistry of carbenes and carbenoids: W. Kirmse, *Carbene Chemistry*; Academic: New York, 1971; F. Z. Dorwald, *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, 1999; *Carbene Chemistry*; ed. by G. Bertrand, Marcel Dekker: New York, 2002; G. Kobrich, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 473; P. J. Stang, *Chem. Rev.*, 1978, **78**, 383; S. D. Burke and P. A. Grieco, *Org. React.*, 1979, **26**, 361; H. F. Schaefer, III, *Acc. Chem. Res.*, 1979, **12**, 288; H. Wynberg and E. W. Meijer, *Org. React.*, 1982, **29**, 1; K. G. Taylor, *Tetrahedron*, 1982, **38**, 2751; A. Oku and T. Harada, *J. Syn. Org. Chem. Jpn.*, 1986, **44**, 736; A. Oku, *J. Syn. Org. Chem. Jpn.*, 1990, **48**, 710; J. Adams and D. M. Spero, *Tetrahedron*, 1991, **47**, 1765; A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223; F. Zaragoza, *Tetrahedron*, 1997, **53**, 3425; W. Kirmse, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1164; M. Braun, *Angew. Chem. Int. Ed.*, 1998, **37**, 430; G. Boche and J. C. Lohrenz, *Chem. Rev.*, 2001, **101**, 697; G. Mehta and S. Muthusamy, *Tetrahedron*, 2002, **58**, 9477; P. Muller, *Acc. Chem. Res.*, 2004, **37**, 243; R. Knorr, *Chem. Rev.*, 2004, **104**, 3795; Z. Zhang and J. Wang, *Tetrahedron*, 2008, **64**, 6577.
2. Some reviews concerning CH insertion reaction: A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385; G. A. Sulikowski, K. L. Cha, and M. M. Sulikowski, *Tetrahedron: Asymmetry*, 1998, **9**, 3145; H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861; H. M. L. Davies and O. Loe, *Synthesis*, 2004, 2595; H. M. L. Davies, *Angew. Chem. Int. Ed.*, 2006, **45**, 6422; Z. Zhang and J. Wang, *Tetrahedron*, 2008, **64**, 6577.
3. T. Satoh, *Chem. Soc. Rev.*, 2007, **36**, 1561; T. Satoh, In *The Chemistry of Organomagnesium Compounds*; ed. by Z. Rappoport and I. Marek, John Wiley and Sons: Chichester, 2008, pp. 717-769; T. Satoh, *J. Syn. Org. Chem. Jpn.*, 2009, **67**, 381; T. Satoh, *YAKUGAKU ZASSHI*, 2009, **129**, 1013.
4. Some reviews concerning carbon-hydrogen insertion reaction: A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385; G. A. Sulikowski, K. L. Cha, and M. M. Sulikowski, *Tetrahedron: Asymmetry*, 1998, **9**, 3145; H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861; H.

M. L. Davies and O. Loe, *Synthesis*, 2004, 2595; H. M. L. Davies, *Angew. Chem. Int. Ed.*, 2006, **45**, 6422; Z. Zhang and J. Wang, *Tetrahedron*, 2008, **64**, 6577.

5. T. Satoh, A. Kondo, and J. Musashi, *Tetrahedron*, 2004, **60**, 5453.
6. T. Satoh, A. Osawa, and A. Kondo, *Tetrahedron Lett.*, 2004, **45**, 6703; T. Satoh, A. Osawa, T. Ohbayashi, and A. Kondo, *Tetrahedron*, 2006, **62**, 7892.
7. T. Ohbayashi, S. Mitsunaga, and T. Satoh, *Tetrahedron Lett.*, 2007, **48**, 7829.
8. S. Mitsunaga, T. Ohbayashi, S. Sugiyama, T. Saitou, M. Tadokoro, and T. Satoh, *Tetrahedron: Asymmetry*, 2009, **20**, 1697.
9. T. Satoh, J. Musashi, and A. Kondo, *Tetrahedron Lett.*, 2005, **46**, 599.
10. T. Satoh, S. Ogata, and D. Wakasugi, *Tetrahedron Lett.*, 2006, **47**, 7249.
11. S. Ogata, H. Saitoh, D. Wakasugi, and T. Satoh, *Tetrahedron*, 2008, **64**, 5711.
12. S. Ogata, S. Masaoka, K. Sakai, and T. Satoh, *Tetrahedron Lett.*, 2007, **48**, 5017.
13. H. Watanabe, S. Ogata, and T. Satoh, *Tetrahedron*, 2010, **66**, 5675.
14. T. Satoh, T. Kuramoto, S. Ogata, H. Watanabe, T. Saitou, M. Tadokoro, and T. Satoh, *Tetrahedron: Asymmetry*, 2010, **21**, 1.
15. T. Satoh, H. Yamashita, and J. Musashi, *Tetrahedron Lett.*, 2007, **48**, 7295.
16. H. Yamashita and T. Satoh, *Tetrahedron*, 2009, **65**, 613.
17. T. Satoh, Y. Awata, S. Ogata, S. Sugiyama, M. Tanaka, and M. Tori, *Tetrahedron Lett.*, 2009, **50**, 1961.
18. T. Satoh, Y. Awata, Y. Kato, S. Ogata, M. Ishigaki, S. Sugiyama, and H. Saitoh, *Tetrahedron*, 2011, **67**, 1102.
19. H. Saitoh, N. Ishida, and T. Satoh, *Tetrahedron Lett.*, 2010, **51**, 633.
20. N. Ishida, H. Saitoh, S. Sugiyama, and T. Satoh, *Tetrahedron*, 2011, **67**, 3081.
21. H. Saitoh and T. Satoh, *Tetrahedron Lett.*, 2010, **51**, 3380.
22. T. Satoh, T. Kurihara, and K. Fujita, *Tetrahedron*, 2001, **57**, 5369.
23. M. Yajima, R. Nonaka, H. Yamashita, and T. Satoh, *Tetrahedron Lett.*, 2009, **50**, 4754.
24. T. Satoh, M. Miura, K. Sakai, and Y. Yokoyama, *Tetrahedron*, 2006, **62**, 4253.
25. Y. Yamada, M. Miura, and T. Satoh, *Tetrahedron Lett.*, 2008, **49**, 169.
26. Y. Yamada, M. Mizuno, S. Nagamoto, and T. Satoh, *Tetrahedron*, 2009, **65**, 10025.
27. T. Satoh, S. Nagamoto, M. Yajima, Y. Yamada, Y. Ohata, and M. Tadokoro, *Tetrahedron Lett.*, 2008, **49**, 5431.
28. T. Satoh, G. Kashiwamura, S. Nagamoto, Y. Sasaki, and S. Sugiyama, *Tetrahedron Lett.*, 2011, **52**, 4468.
29. T. Satoh, T. Noguchi, and T. Miyagawa, *Tetrahedron Lett.*, 2008, **49**, 5689.

30. T. Miyagawa, T. Tatenuma, M. Tadokoro, and T. Satoh, *Tetrahedron*, 2008, **64**, 5279.
31. H. Momochi, T. Noguchi, T. Miyagawa, N. Ogawa, M. Tadokoro, and T. Satoh, *Tetrahedron Lett.*, 2011, **52**, 3016.
32. T. Noguchi, T. Miyagawa, and T. Satoh, *Tetrahedron: Asymmetry*, 2009, **20**, 2073.
33. T. Satoh, S. Ikeda, T. Miyagawa, and T. Noguchi, *Tetrahedron Lett.*, 2010, **51**, 1955.
34. T. Satoh, T. Tsuru, S. Ikeda, T. Miyagawa, H. Momochi, and T. Kimura, *Tetrahedron*, submitted.
35. T. Satoh, T. Kasuya, T. Miyagawa, and N. Nakaya, *Synlett*, 2010, 286.
36. T. Satoh, T. Kasuya, M. Ishigaki, M. Inumaru, T. Miyagawa, N. Nakaya, and S. Sugiyama, *Synthesis*, 2011, 397.
37. M. Ishigaki, M. Inumaru, and T. Satoh, *Tetrahedron Lett.*, 2011, **52**, 5563.
38. N. Nakaya, S. Sugiyama, and T. Satoh, *Tetrahedron Lett.*, 2009, **50**, 4212.
39. T. Satoh, K. Takano, H. Ota, H. Someya, K. Matsuda, and M. Koyama, *Tetrahedron*, 1998, **54**, 5557.
40. T. Satoh, T. Sakamoto, M. Watanabe, and K. Takano, *Chem. Pharm. Bull.*, 2003, **51**, 966.
41. J. Sakurada and T. Satoh, *Tetrahedron*, 2007, **63**, 3806.
42. T. Satoh, N. Mori, and K. Obuchi, *Tetrahedron Lett.*, 2007, **48**, 6453.
43. N. Mori, K. Obuchi, T. Katae, J. Sakurada, and T. Satoh, *Tetrahedron*, 2009, **65**, 3509.
44. T. Satoh, H. Kaneta, A. Matsushima, and M. Yajima, *Tetrahedron Lett.*, 2009, **50**, 6280.
45. T. Satoh, *J. Syn. Org. Chem. Jpn.*, 2009, **67**, 381.
46. T. Satoh, S. Tanaka, and N. Asakawa, *Tetrahedron Lett.*, 2006, **47**, 6769.
47. S. Tanaka, T. Anai, M. Tadokoro, and T. Satoh, *Tetrahedron*, 2008, **64**, 7199.
48. S. Fukuda, K. Tsuji, J. Musashi, R. Nonaka, T. Kimura, and T. Satoh, *Synthesis*, 2011, 3615.

Professor Tsuyoshi Satoh was born in 1947 in Fukushima, Japan. He graduated in pharmaceutical chemistry from Tokyo University of Science (TUS) in 1970. He then moved to Hokkaido University and received MS degree in 1972 under the guidance of Professor Y. Kanaoka. He joined the Faculty of Pharmaceutical Science, TUS, as Research Associate and was promoted to Lecturer in 1989. He received his PhD from Hokkaido University in the field of total synthesis of natural products in 1979. In 1981, he spent one year as a postdoctoral fellow at the University of Wisconsin-Madison, where he joined the group of Professor Barry M. Trost and studied Pd-TMM complex in organic synthesis. In 1996, he moved to the Department of Chemistry, Faculty of Science, TUS, as Associate Professor and was promoted to Professor in 2000. He was awarded the 1991 Pharmaceutical Society of Japan (PSJ) Award for Young Scientists, Tetrahedron: Asymmetry Most Cited Paper Award (2006), and the 2009 PSJ Award for Divisional Scientific Contributions. His current research interest focus is on organosulfur chemistry, organomagnesium chemistry, carbanion, chemistry of carbenoids especially magnesium carbenoids in organic synthesis, asymmetric synthesis, and strained molecules in organic synthesis.