Recent advances in the chemistry of magnesium carbenoids

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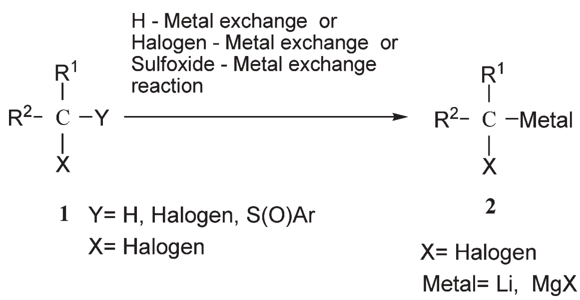
This *tutorial review* deals with recent advances in the chemistry and synthetic use of magnesium carbenoids. The reactivity of traditional carbenoids (α-haloalkyllithium species) was successfully reduced by using magnesium as the metal instead of lithium. Properties of these relatively stable carbenoids, magnesium carbenoids, were widely investigated and it was found that the magnesium carbenoids have very interesting reactivity toward several nucleophiles. The magnesium carbenoids, magnesium cyclopropylidenes, magnesium alkylidene carbenoids, and magnesium β-oxido carbenoids are generated from α-chloroalkyl (or α-chloroalkenyl) aryl sulfoxides with a Grignard reagent at low temperature by sulfoxide–magnesium exchange reaction. The stability of the generated magnesium carbenoids and several new reactions based on the electrophilicity of the magnesium carbenoids, including 1,3-CH insertion, are reviewed. Magnesium carbenoids open up the new world of the chemistry of carbenoids.

1 Introduction

Carbenes and carbenoids[1] have long been recognized as a highly reactive carbon species and are frequently used as useful intermediates in organic synthesis.[2] From the viewpoint of synthetic organic chemistry, however, many carbenes are relatively short-lived[3] and are too reactive to control. Carbenoids **2** have been generated from alkylhalides (**1**; Y = H or halogen) by H–Metal or halogen–metal exchange reactions (eqn (1)). Especially, lithium carbenoids (**2**; metal = Li) were generated from alkylhalides with butyllithium; however, they are so reactive that usually the H–Li or halogen–Li exchange reaction must be conducted at below −90 °C. On the other hand, from recent cumulative investigations, magnesium carbenoids (**2**; metal = MgX) could be generated from alkyliodides (**1**; Y = I) or sulfoxides (**1**; Y = S(O)Ar) by iodine–magnesium or sulfoxide–magnesium exchange reaction and were found to be much more stable compared with the lithium carbenoids. As a result, magnesium carbenoids can be generated at around −78 °C and are relatively easy to handle and they were found to show quite interesting reactivity. In this review, recent advances in the chemistry of magnesium carbenoids will be discussed.



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Professor Tsuyoshi Satoh was born in 1947 in Fukushima, Japan. He studied pharmaceutical sciences at Tokyo University of Science where he received the BS degree in 1970. He then moved to Hokkaido University and received the MS degree in 1972 under the guidance of Professor Y. Kanaoka. That same year, he joined the Faculty of Pharmaceutical Science, Tokyo University of Science, 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 the Pd–TMM complex in organic synthesis. In 1996, he moved to the Department of Chemistry, Faculty of Science, Tokyo University of Science, as Associate Professor and was promoted to Professor in 2000. He was awarded the 1991 Pharmaceutical Society of Japan Award for Young Scientists. His current research interest focus is on organosulfur chemistry, carbanion chemistry, chemistry of carbenoids especially magnesium carbenoids in organic synthesis, asymmetric synthesis, and strained molecules in organic synthesis.

2 Generation, reactivity, and synthetic uses of magnesium carbenoids

The halogen–metal exchange reaction is well known for the generation of alkyl-, alkenyl-, and arylmetals from the corresponding halides with alkylmetals. Especially the bromine– or iodine–lithium exchange reactions are widely used for generation of lithium carbanions or lithium carbenoids. On the other hand, a quite limited number of examples were reported for generation of magnesium carbenoids by halogen–magnesium exchange reaction before 2000. For example, bromochloromethylmagnesium chloride **3** was generated from chlorodibromomethane in THF with isopropylmagnesium chloride at −95 °C by bromine–magnesium exchange reaction. Diiodomethylmagnesium chloride **4** was also derived from triiodomethane with isopropylmagnesium chloride at −85 °C by iodine–magnesium exchange reaction (eqn (2)).[4]

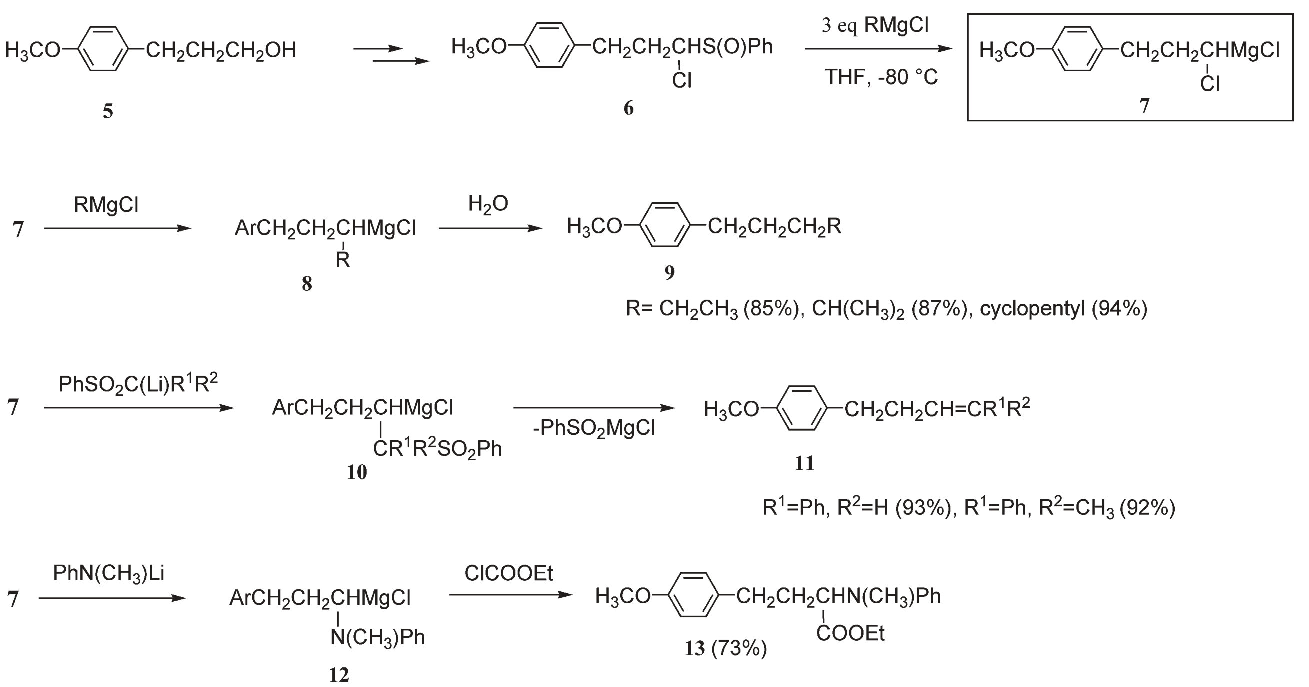
$$HCBr_2Cl \xrightarrow[THF, -95\ ^\circ C]{i-PrMgCl} \underset{\mathbf{3}}{HCBr(Cl)MgCl}$$
$$HCI_3 \xrightarrow[THF, -85\ ^\circ C]{i-PrMgCl} \underset{\mathbf{4}}{HCI_2MgCl} \qquad (2)$$

The magnesium carbenoids (**3** and **4**) were found to be sufficiently stable at low temperature and could be reacted with electrophiles.[4] However, recently, the magnesium carbenoids were found to be much more conveniently generated from α-chloroalkyl (or α-chloroalkenyl) aryl sulfoxides[5] at low temperature by sulfoxide–magnesium exchange reaction.[6] For instance, 1-chloroalkyl aryl sulfoxide **6** was quite easily prepared from alcohol **5** in three steps in high overall yield.[7] Treatment of the sulfoxide **6** with a Grignard reagent (usually isopropylmagnesium chloride) resulted in the formation of magnesium carbenoid **7** instantaneously even at −80 °C. The generated magnesium carbenoid **7** was found to be stable at lower than −60 °C for over 30 min (Scheme 1).[7]

Carbenoids have both a nucleophilic and an electrophilic nature. This is one of the most striking characteristics of carbenoids. Especially, electrophilic reaction of the magnesium carbenoids with carbon and nitrogen nucleophiles has recently received much attention and various new interesting synthetic methods have appeared. The reaction of a Grignard reagent with magnesium carbenoid **7**, derived from **6** by the sulfoxide–magnesium exchange reaction, was reported (Scheme 1).[7] Thus, treatment of 1-chloroalkyl phenyl sulfoxide **6** with 5 eq. of EtMgCl at −80 °C followed by slowly warming the reaction to −30 °C gave an ethylated product (**9**, R = CH_2CH_3) in 85% yield. This reaction proceeds *via* the new alkylmagnesium **8** derived by substitution of the chlorine atom of carbenoid **7** with used EtMgCl. Magnesium carbenoids were found to be reactive with the Grignard reagents used to afford several alkylated products **9** in good yields, as indicated in Scheme 1. Primary and secondary Grignard reagents reacted well with carbenoid **7**; however, *t*-BuMgCl did not react at all with the 1-chloroalkyl phenyl sulfoxide **6**.

Magnesium carbenoids react not only with Grignard reagents but also with other carbanions such as lithium α-sulfonyl carbanions to afford olefins. Thus, magnesium carbenoid **7** was generated from 1-chloroalkyl phenyl sulfoxide **6** in THF at −65 °C with 2.8 eq. of *i*-PrMgCl. To this solution was added lithium α-sulfonyl carbanion and the reaction mixture was allowed to warm to −40 °C. 1,2-Disubstituted and 1,1,2-trisubstituted olefins **11** were obtained in good yields through the intermediates **10**.

The electrophilic reaction of the magnesium carbenoids with *N*-lithio arylamines was found to give non-stabilized α-amino-substituted carbanions.[8] Thus, treatment of magnesium carbenoid **7** with 3.5 eq. of *N*-lithio *N*-methylaniline at −70 °C followed by warming the reaction mixture slowly to −40 °C gave a non-stabilized α-amino-substituted carbanion (α-amino-substituted Grignard reagent) **12** in good yield. The generation of **12** was confirmed by quenching the reaction with deuterated methanol. This reaction gave *N*-methylaniline having an α-deuterated alkyl group in 77% yield with 91%



Scheme 1

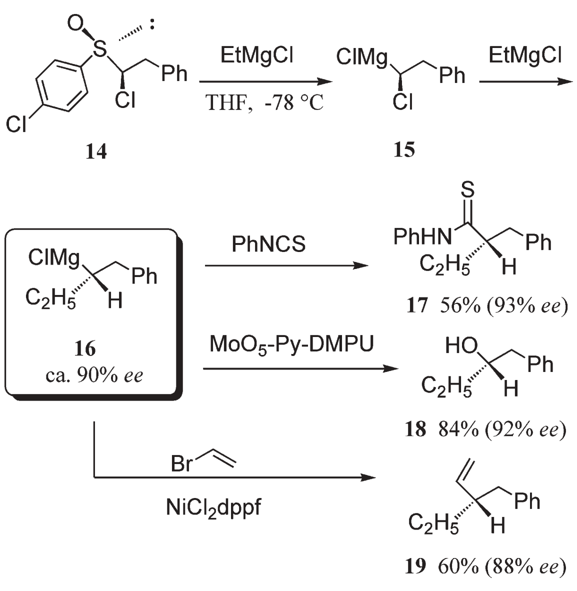
deuterium incorporation. Generation of the α-amino-substituted carbanions is well recognized to be quite difficult from non-activated amines.[9] The results obtained in this study are highly notable as a new method for generation of non-stabilized α-amino carbanions.

Reaction of α-amino-substituted carbanion **12** with ethyl chloroformate was found to give α-amino acid derivative **13** in 73% yield. This is a very interesting unprecedented one-pot synthesis of an α-amino acid derivative from 1-chloroalkyl aryl sulfoxide. The synthesis of several α-amino acid esters, including glycine derivatives, by this method is reported.[8]

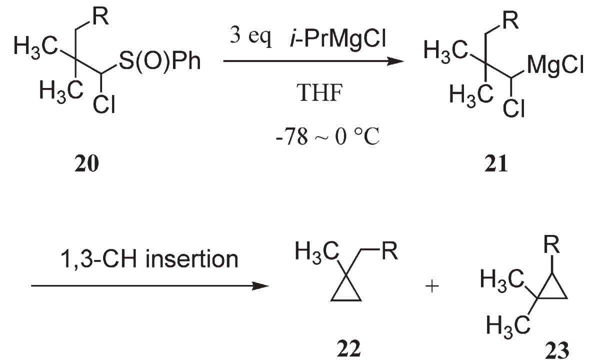
As configuration of the magnesium carbenoids is rather stable at low temperature, chiral Grignard reagents having over 90% ee could be generated from optically active 1-chloroalkyl aryl sulfoxides (Scheme 2).[10–12]

Treatment of the optically pure 1-chloroalkyl aryl sulfoxide **14** with excess EtMgCl gave initially the optically active magnesium carbenoid **15** by the sulfoxide–magnesium exchange reaction. The electrophilic reaction of carbenoid **15** with EtMgCl gave the optically active secondary Grignard reagent **16** with inversion of configuration of the chiral carbon. Quenching of this reaction with phenylisothiocyanate gave thioamide **17** in 56% yield with 93% ee. Quite interestingly, from this experiment it appeared that the secondary Grignard reagent **16** is configurationally stable at −78 °C. Oxidation of **16** with molybdenum peroxide gave alcohol **18** with retention of the configuration and the enantiomeric purity of **16** was retained. Kumada–Corriu coupling of **16** with vinyl bromide in the presence of Ni-catalyst gave a coupling product **19** with full retention of the configuration.[11]

The carbon–hydrogen insertion (CH insertion) is one of the most striking reactions of carbenes and carbenoids. The reaction is quite interesting and very useful for construction of molecules, because formation of a carbon–carbon bond between a carbene (or carbenoid) carbon and inactivated carbon is realized. The author studied the CH insertion of magnesium carbenoids starting from 1-chloroalkyl phenyl sulfoxides **20** as representative examples (Scheme 3).[13]



Scheme 2



R	**22** Yield/%	**23** Yield/%
1-Naph	65	32
OTHP	97	0
$OSiMe_2Bu$-*t*	85	0
$OCH_2OCH_2CH_2OCH_3$	89	0

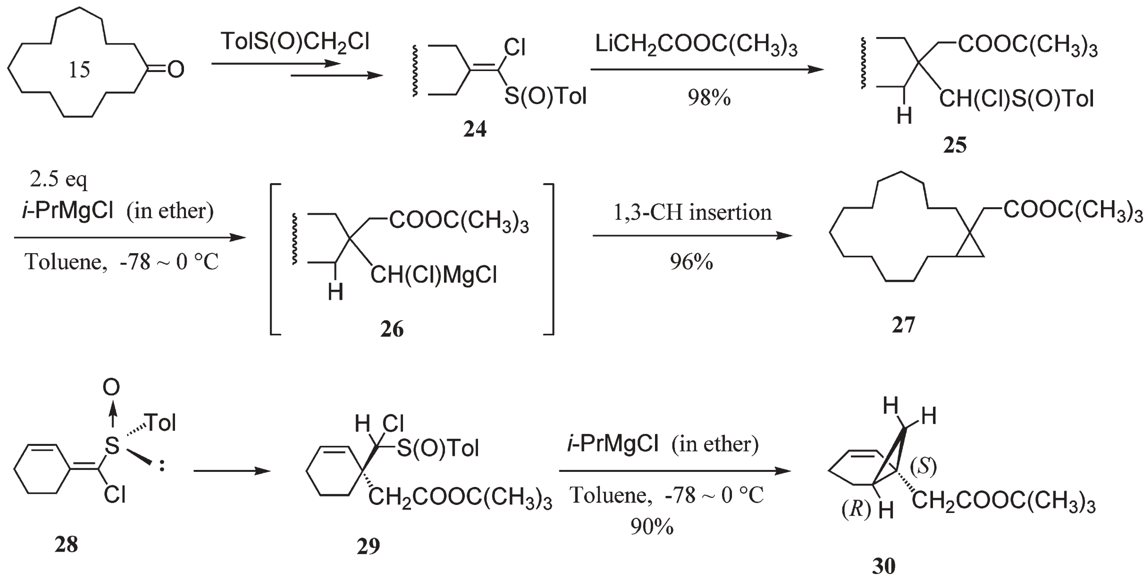
Scheme 3

Thus, 1-chloroalkyl phenyl sulfoxide **20** was treated with 3 eq. of *i*-PrMgCl in THF at −78 °C and the reaction mixture was slowly allowed to warm to 0 °C resulting in the formation of cyclopropanes **22** and **23** in good to high yields. The intermediate of this reaction is magnesium carbenoid **21** and 1,3-CH insertion took place between the carbenoid carbon and the methyl- or the methylene-carbon. Interestingly, when the substituent R has an oxygen functional group; the CH insertion exclusively took place between methyl-carbon to afford cyclopropane **22** as the sole product. As recognized from the results in Scheme 3, the CH insertion of magnesium carbenoids gives high yields of cyclopropanes and the conditions of the reaction are quite mild.

A very interesting synthesis of bicyclo[*n*.1.0]alkanes from cyclic ketones *via* the magnesium carbenoid 1,3-CH insertion as a key reaction was reported (Scheme 4).[14] For example, 1-chlorovinyl *p*-tolyl sulfoxide **24** was synthesized from cyclopentadecanone and chloromethyl *p*-tolyl sulfoxide in three steps in high overall yield. Lithium enolate of *tert*-butyl acetate was added to **24** to give an adduct **25** in quantitative yield. α-Chlorosulfoxide **25** was treated with *i*-PrMgCl (in ether) in toluene as the solvent of the reaction at −78 °C and the reaction mixture was slowly allowed to warm to 0 °C to afford bicyclo[13.1.0]hexadecane derivative **27** in 96% yield through magnesium carbenoid **26** as an intermediate.

It is worth noting that use of the *i*-PrMgCl in ether (not in THF) and toluene as the solvent for the reaction was reported to be essential to this reaction. Otherwise, a protonated product of magnesium carbenoid **26** was obtained as a by-product, which was very difficult to separate from the desired product **27**. Another interesting result of this reaction was that the 1,3-CH insertion reaction is highly regioselective.

Starting from optically active 1-chlorovinyl *p*-tolyl sulfoxide **28** derived from 2-cyclohexenone, an asymmetric synthesis of a

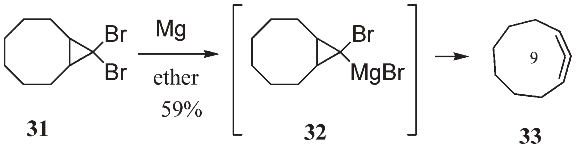


Scheme 4

cyclopropane derivative was realized. Addition reaction of lithium enolate of *tert*-butyl acetate with **28** gave adduct **29** in 96% yield with over 99% ee as a single product. Treatment of this α-chloroalkyl sulfoxide **29** with *i*-PrMgCl in a similar way as described above afforded optically pure (1*S*,6*R*)-bicyclo-[4.1.0]hept-2-ene **30** in 90% yield.

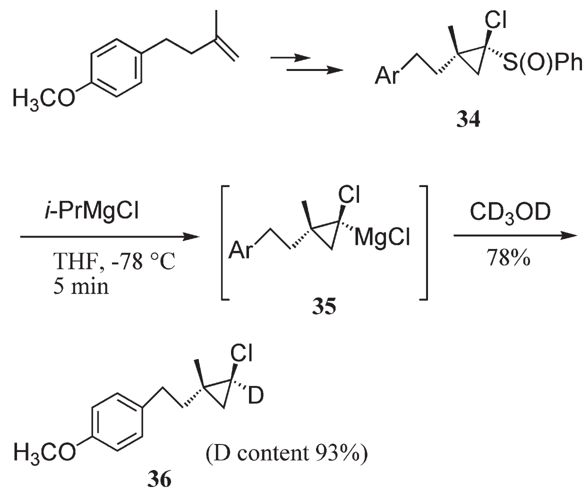
3 Magnesium cyclopropylidenes

Cyclopropylidenes (carbenacyclopropanes) are the carbenes or carbenoids of cyclopropanes and also are known as the highly reactive intermediates of the reaction of 1,1-dihalocyclopropanes with alkylmetals giving allenes. This reaction is now called the Doering–LaFlamme allene synthesis. For example, 9,9-dibromobicyclo[6.1.0]nonane **31**, derived from cyclooctene, was treated with magnesium in ether under reflux to give 1,2-cyclononadiene **33** in 59% yield. Magnesium cyclopropylidene **32** is thought to be the intermediate of this reaction (eqn (3));[15] however, the stability and chemical nature of the magnesium cyclopropylidenes have not been investigated.



(3)

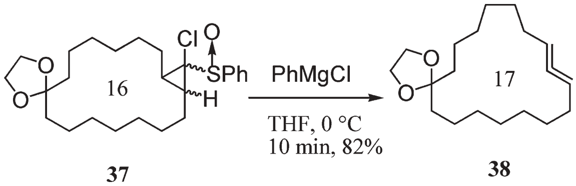
In 2001, the author's group studied the generation of magnesium cyclopropylidenes from 1-chlorocyclopropyl phenyl sulfoxides at −78 °C by the sulfoxide–magnesium exchange reaction.[16] At first, 1-chlorocyclopropyl phenyl sulfoxide **34** was synthesized from an olefin in three steps in good yield. Treatment of sulfoxide **34** with 2.5 eq. of *i*-PrMgCl in THF at −78 °C for 5 min followed by quenching with CD_3OD afforded a deuterated chlorocyclopropane **36** in 78% yield with high deuterium incorporation. From this experiment, it was proved that the intermediate of the reaction is magnesium cyclopropylidene **35** (eqn (4)).



(4)

In addition, it was concluded that magnesium cyclopropylidene **35** is stable at below −60 °C for at least 3 h and also the configuration of the carbenoid carbon is fairly stable at below −60 °C.[16]

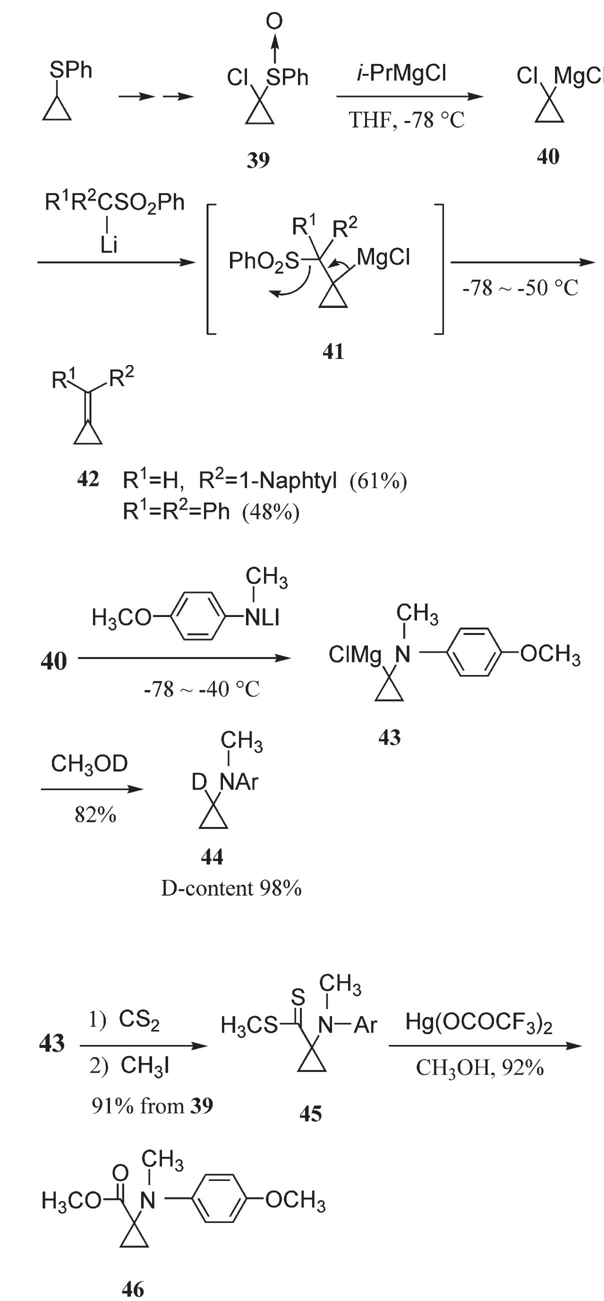
The magnesium cyclopropylidenes were found to be unstable around 0 °C; for example, treatment of α-chlorocyclopropyl phenyl sulfoxide **37**, derived from the corresponding olefin, with 2.5 eq. of PhMgCl at 0 °C for 10 min to afford one-carbon ring-expanded allene **38** in good yield *via* the magnesium cyclopropylidenes (eqn (5)).[16] This reaction provided a good method for synthesis of allenes from olefins with one-carbon elongation.



(5)

An interesting reaction using the electrophilic reaction of magnesium cyclopropylidenes with lithium α-sulfonyl carbanion giving alkylidenecyclopropanes was reported (Scheme 5).[17] 1-Chlorocyclopropyl phenyl sulfoxide **39** was synthesized from commercially available cyclopropyl phenyl sulfoxide in 93% overall yield. Sulfoxide **39** was treated with 2.5 eq. of *i*-PrMgCl at −78 °C and the sulfoxide–magnesium exchange reaction was found to take place instantaneously to give magnesium cyclopropylidene **40**. To this carbenoid, three equivalents of a lithium α-sulfonyl carbanion was added and the reaction mixture was allowed to warm to −50 °C to give alkylidene cyclopropane **42** in moderate yield.

The proposed mechanism of this reaction is as follows. First, S_N2-type nucleophilic substitution reaction of **40** with the nucleophile, lithium α-sulfonyl carbanion, takes place to give alkylmagnesium having a sulfonyl group at the β-position **41**. β-Elimination of magnesium sulfinate from the intermediate then occurs to give alkylidene cyclopropane **42**.



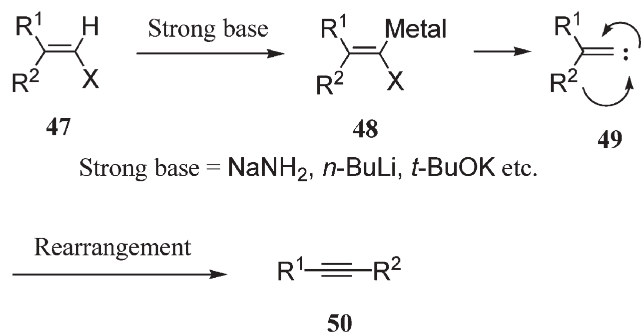
Scheme 5

The electrophilic reaction of magnesium cyclopropylidene **40** with *N*-lithioarylamines was reported (Scheme 5).[18] Thus, electrophilic reaction of magnesium cyclopropylidene **40** derived from **39** with *N*-lithio *N*-methyl *p*-anisidine resulted in the formation of α-amino-substituted cyclopropylmagnesium **43** in good yield. Quenching of this reaction with CH_3OD gave α-deuterated *N*-cyclopropyl-*N*-methyl *p*-anisidine **44** in 82% yield with 98% D-content. The reaction of **40** with *N*-methylaniline, *p*-chloro-*N*-methylaniline, and *N*-benzyl-*p*-anisidine gave 60–67% yield of the desired *N*-cyclopropyl arylamines. Diphenylamine gave the desired product; however, the yield was not satisfactory.

Reactivity of the α-amino-substituted cyclopropylmagnesium **43** with some electrophiles was investigated. Cyclopropylmagnesium **43** was found to have low nucleophilicity and, for example, reaction with benzaldehyde gave only 40% yield of the adduct. The reaction of **43** with ethyl chloroformate gave a maximum 20% yield of the desired ethoxycarbonylated product. On the other hand, the reaction of **43** with carbon disulfide followed by iodomethane gave thioester **45** in high yield (Scheme 5). Methanolysis of the dithioester **45** in methanol with excess $Hg(OCOCF_3)_2$ gave a cyclopropane α-amino acid derivative **46** in high yield.

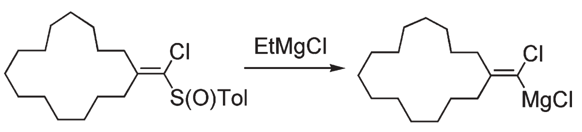
4 Magnesium alkylidene carbenoids

Alkylidene carbenoids are the carbenoids of olefinic carbon and are known as very interesting reactive intermediates.[19] The most famous reaction *via* the alkylidene carbenoids as the intermediate is the Fritsch–Buttenberg–Wiechell rearrangement (eqn (6)).



(6)

Thus, treatment of 1-haloalkene **47** with a strong base resulted in the formation of alkylidene carbenoid **48** by the hydrogen–metal exchange reaction. The metal in **48** is usually Na, Li, or K. The alkylidene carbenoid **48** is highly unstable and elimination of Metal–X resulted in the formation of alkylidene carbene **49**. The Fritsch–Buttenberg–Wiechell rearrangement then takes place to afford acetylene **50**. As the alkylidene carbenoid **48** was usually generated at room temperature or higher, the real property of the alkylidene carbenoid was unclear until recently.



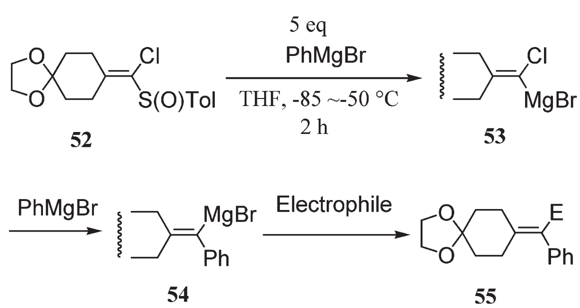
(7)

24 **51**

Reports for generation and property of lithium- and magnesium alkylidene carbenoids from 1-chlorovinyl aryl sulfoxides by sulfoxide–methal exchange reaction at low temperature were published from our research group (eqn (7)).[20,21] Treatment of 1-chlorovinyl *p*-tolyl sulfoxide **24**, mentioned above, with EtMgCl in THF at −78 °C resulted in the formation of magnesium alkylidene carbenoid **51** instantaneously by the sulfoxide–magnesium exchange reaction. The formation of carbenoid **51** was confirmed by quenching the reaction with CD_3OD to afford deuterated chloroalkene in high yield. Moreover, magnesium alkylidene carbenoid **51** was found to be stable at below −78 °C for at least 30 min. Interestingly, the Fritsch–Buttenberg–Wiechell rearrangement was rarely observed from the magnesium alkylidene carbenoids derived from ketones.[21]

From the viewpoint of synthetic organic chemistry, the electrophilic nature of the magnesium alkylidene carbenoids is much more interesting than their nucleophilic nature. The author's group found that treatment of 1-chlorovinyl *p*-tolyl sulfoxide **52** with excess PhMgBr in THF at −85 to −50 °C for 2 h followed by CD_3OD gave a phenylated and deuterated olefin (**55**, E = D) in 80% yield with perfect deuterium incorporation (Scheme 6).[21b]

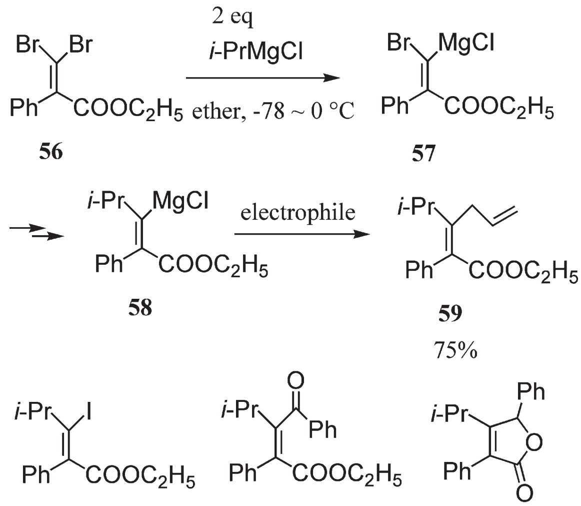
The reaction proceeded as follows. At first, the sulfoxide–magnesium exchange reaction of **52** gave magnesium alkylidene carbenoid **53**. Based on the electrophilic nature of carbenoid, nucleophilic substitution of **53** on the sp^2 carbon



Electrophile	**55** / Yield
CD_3OD	80[a)]
$CH_3CH_2CH_2CHO$	81
ClCOOEt	65
I_2	53
PhNCO	87

a) D-content 99%.

Scheme 6



60 82% **61** 61% **62** 56%

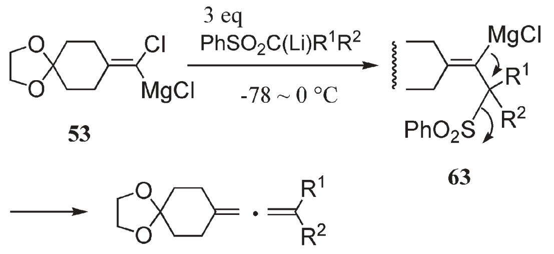
Scheme 7

with PhMgBr resulted in the formation of alkenyl Grignard reagent **54**. Finally, the carbanion was quenched with CD_3OD to afford the deuterated olefin **55** (E = D). These reactions resulted in a quite interesting double substitution of sulfinyl- and chloro groups to phenyl- and deuterio groups on the olefinic sp^2 carbon in one-pot. This reaction was applied to a new method for synthesis of tetra-substituted olefins from 1-chlorovinyl *p*-tolyl sulfoxides and the selected results are summarized in Scheme 6.

A similar reaction was reported by Knochel and Marek (Scheme 7).[22] Thus, dibromide **56** was treated with 2 equiv. of *i*-PrMgCl at −78 °C and the reaction mixture was warmed to 0 °C to give a functionalized alkenyl Grignard reagent **58** through magnesium alkylidene carbenoid **57**. Trapping of the alkenyl Grignard reagent **58** with allyl bromide in the presence of CuCN–2LiCl gave the allylated olefin **59** in 75% yield. The same reaction of **58** with iodine, benzoyl chloride, and benzaldehyde gave olefins **60**, **61**, and **62** in moderate to good yields.

The electrophilic reaction of the magnesium alkylidene carbenoids with nucleophiles other than the Grignard reagent that is used for generation of the carbenoids can be carried out. For example, treatment of magnesium alkylidene carbenoid **53**, derived from **52**, with lithium α-sulfonyl carbanion afforded allenes **64** in moderated yields (Scheme 8).[23] A proposed mechanism is as follows. First, the lithium α-sulfonyl carbanion attacks the electrophilic carbenoid carbon to give the vinylmagnesium intermediate **63**. As the sulfonyl group is a good leaving group, β-elimination takes place to afford the allenes **64**.

A very interesting direct alkenylation of arylamines at the *ortho*-position by the reaction of magnesium alkylidene carbenoids with *N*-lithio arylamines was reported from the author's group (Table 1).[24] Magnesium alkylidene carbenoid **53**, derived from **52** in toluene, was treated with three equiv. of *N*-lithio aniline at −78 °C and the reaction mixture was gradually allowed to warm to −10 °C to give *ortho*-alkenylated



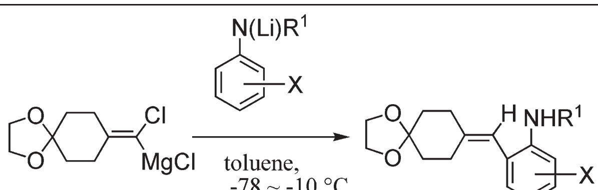
53 **63**

64 R^1=Ph, R^2=H 65%
R^1=1-Naphtyl, R^2=H 51%
R^1=Vinyl, R^2=H 51%
R^1=CH_2CH_2Ar, R^2=H 42%
R^1=CCC_5H_{11}, R^2=H 65%
R^1=Ph, R^2=Ph 41%

Scheme 8

aniline in 49% yield. Toluene was found to be the best solvent for this reaction. The generality of this unprecedented reaction was investigated and the selected results are summarized in Table 1. 2-Methylaniline gave only an *ortho*-alkenylated product and 2,6-dimethylaniline gave no alkenylated product. These results indicated that this reaction only gives *ortho*-alkenylated products. Interestingly, the reaction with 1-aminonaphthalene and 1-aminoanthracene gave much better yields.

Table 1 Synthesis of *ortho*-alkenylated arylamines **65** by the reaction of magnesium alkylidene carbenoid **53** with *N*-lithio arylamines



53 **65**

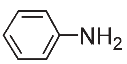
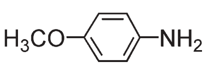
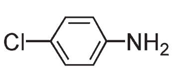
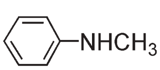
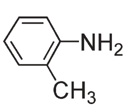
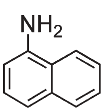
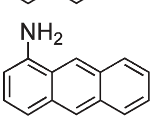
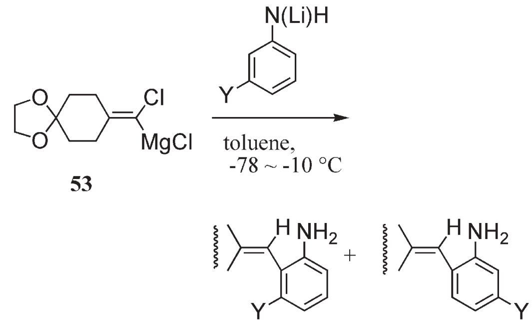
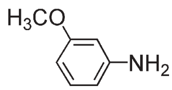
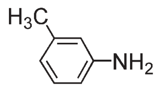
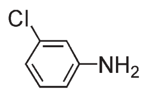
Arylamine	Yield%
	49
	44
	28
	38
	32
	66
	60

Table 2 Synthesis of *ortho*-alkenylated arylamines **66** and **67** by the reaction of magnesium alkylidene carbenoid **53** with *meta*-substituted *N*-lithio arylamines



53 **66** **67**

	66 and **67**	
Arylamine	Yield%	**66** : **67**
	43	30 : 13
	33	19 : 14
	38	25 : 13

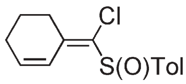
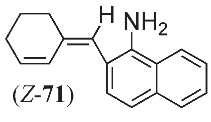
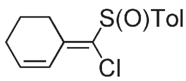
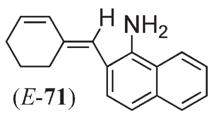
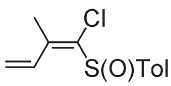
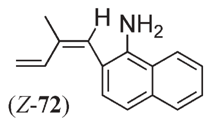
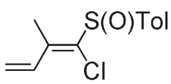
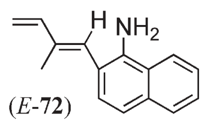
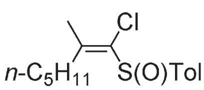
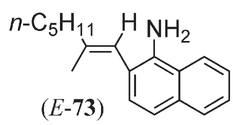
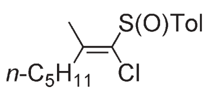
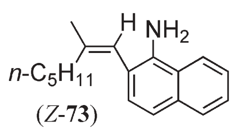
Very interesting results were obtained from the reaction of the magnesium alkylidene carbenoids with *meta*-substituted arylamines (Table 2).[24b] The reaction of magnesium alkylidene carbenoid **53** with three *meta*-substituted anilines was carried out and the results are summarized in Table 2. The reaction of **53** with *m*-anisidine gave two products (ratio was 30 : 13) in 43% yield, and the main product was found to have the alkenyl group at a more hindered position **66**. As shown in Table 2, although the ratio is somewhat variable, all the other *meta*-substituted anilines also gave more hindered alkenylated compounds as the main products.

A theoretical study of this interesting regioselectivity by calculations using the Gaussian 98 program was performed.[24b] Thus, electrostatic potential-derived charges using the CHelpG scheme of Breneman were calculated with the structures optimized at the MP2/6-31(+)G* level and the more negative charge was found on the carbon-2 in the most stable conformer.

The stereochemistry of this reaction is also quite interesting. Thus, both geometrical isomers of 1-chlorovinyl *p*-tolyl sulfoxides (**68**–**70**) were synthesized from 2-cyclohexenone, methyl vinyl ketone, and 2-heptanone, and the corresponding magnesium alkylidene carbenoids were generated and treated with *N*-lithio 1-aminonaphthalene. The results are summarized in Table 3.

Interestingly, the reaction of the magnesium alkylidene carbenoids derived from *E*-**68** and *Z*-**68** with *N*-lithio 1-aminonaphthalene gave *Z*-*ortho*-alkenylated 1-aminonaphthalene (*Z*-**71**) and *E*-*ortho*-alkenylated 1-aminonaphthalene (*E*-**71**), respectively, with high stereospecificity (entries 1

Table 3 The reaction of the magnesium alkylidene carbenoids derived from *E*- and *Z*-1-chlorovinyl *p*-tolyl sulfoxides with *N*-lithio 1-aminonaphthalene

Entry	1-Chloroviny *p*-tolyl sulfoxide	Product	*E* : *Z*	Yield%
1	 (*E*-**68**)	 (*Z*-**71**)	3 : 97	65
2	 (*Z*-**68**)	 (*E*-**71**)	95 : 5	71
3	 (*E*-**69**)	 (*Z*-**72**)	4 : 96	68
4	 (*Z*-**69**)	 (*E*-**72**)	94 : 6	62
5	 (*E*-**70**)	 (*E*-**73**)	44 : 56	54
6	 (*Z*-**70**)	 (*Z*-**73**)	34 : 66	55

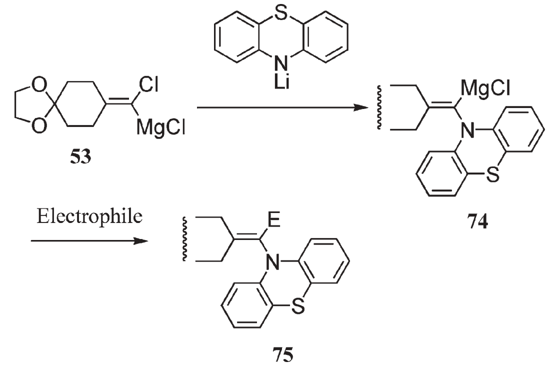
and 2). The same results were obtained from *E*-**69** and *Z*-**69** with *N*-lithio 1-aminonaphthalene (entries 3 and 4). Obviously, the *N*-lithio 1-aminonaphthalene attacks backside to the chlorine atom to give the products stereospecifically with inversion of the configuration of the sp^2 carbon.

On the other hand, when this reaction was carried out with the 1-chlorovinyl *p*-tolyl sulfoxide derived from unsymmetrical dialkyl ketone **70** with *N*-lithio 1-aminonaphthalene (entries 5 and 6), *Z-ortho*-alkenylated 1-aminonaphthalene (*Z*-**73**) was obtained as a main product from both vinyl sulfoxides with low stereoselectivity. The stereospecificity and stereoselectivity mentioned above are explained from the high configurational stability of the magnesium carbenoids generated from 1-chlorovinyl *p*-tolyl sulfoxides derived from α,β-unsaturated ketones. For better understanding of the structure and the substitution reactions of the magnesium alkylidene carbenoids, computational studies were performed.[24b]

The magnesium alkylidene carbenoids were found to be reactive with some other nucleophiles to give new alkenylmagnesium compounds which could be trapped with electrophiles. As a whole, novel methods for synthesis of tri- or tetra-substituted olefins from the 1-chlorovinyl *p*-tolyl sulfoxides in one-pot were realized (Table 4).

For example, treatment of magnesium alkylidene carbenoid **53** with *N*-lithio phenothiazine in toluene in the presence of ether resulted in the formation of *N*-alkenylated phenothiazine

Table 4 Synthesis of phenothiazine having a fully substituted olefin on the nitrogen **75** by the reaction of magnesium alkylidene carbenoid **53** with *N*-litho phenothiazine followed by some electrophiles



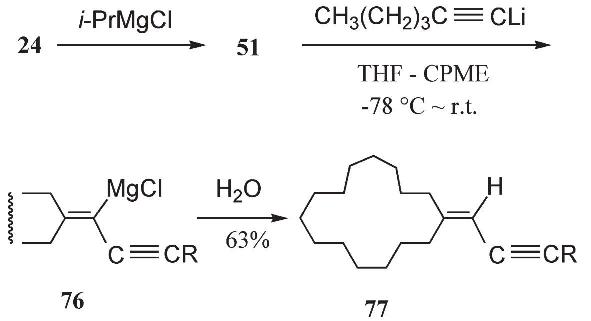
Electrophile	**75** E	Yield%
CH_3OD	D	71[a]
CH_3I	CH_3	62[b]
CH_3CH_2I	CH_3CH_2	55[b]
CH_2=$CHCH_2I$	CH_2=$CHCH_2$	63[b]
$PhCH_2Br$	$PhCH_2$	30[b]
PhCOCl	PhCO	59[b]
PhNCO	PhNHCO	39

[a] Deuterium content 98%. [b] The reaction was carried out with CuI as a catalyst.

75 (E = H) in 71% yield through the alkenylmagnesium intermediate **74** (Table 4).[25] The generality of this reaction was investigated and indole, indazole, pyrazole, and phenoxazine were found to give the desired *N*-alkenylated products in moderate to good yields. From the viewpoint of synthetic organic chemistry, trapping the alkenylmagnesium intermediate **74** with electrophiles is very interesting. If the intermediates could be trapped with electrophiles, the reaction should provide a novel method for synthesis of nitrogen-containing heterocycles having a fully substituted olefin on the nitrogen. This expectation proved to be possible (Table 4).[25]

The results for the trapping of this alkenylmagnesium with several electrophiles are summarized in Table 4. Quenching of this reaction with deuterio methanol gave the olefin having a deuterium (**75**; E = D) in 71% yield and the deuterium incorporation was 98%. The reaction with iodomethane did not take place; however, using 5 mol% of CuI as a catalyst at room temperature resulted in the formation of the methylated olefin in 62% yield. The alkylation and allylation required CuI as a catalyst. Benzoyl chloride and phenyl isocyanate reacted with the alkenylmagnesium intermediate **74** to give the desired products **75**.

Lithium acetylides were found to react with magnesium alkylidene carbenoids to afford enynes (eqn (8)).[26] Thus, magnesium alkylidene carbenoid **51** was generated from 1-chlorovinyl *p*-tolyl sulfoxide **24** and it was reacted with lithium carbanion of 1-hexyne (3 equiv.) to give a conjugated enyne **77** in 63% yield through alkenylmagnesium intermediate **76**. Unfortunately, the yields of the reactions and the trapping of the intermediate **76** with electrophiles did not give satisfactory results.[26]



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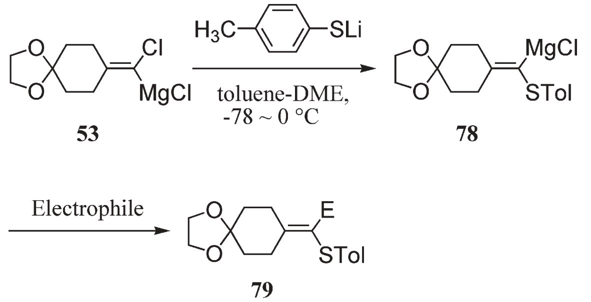


(9)

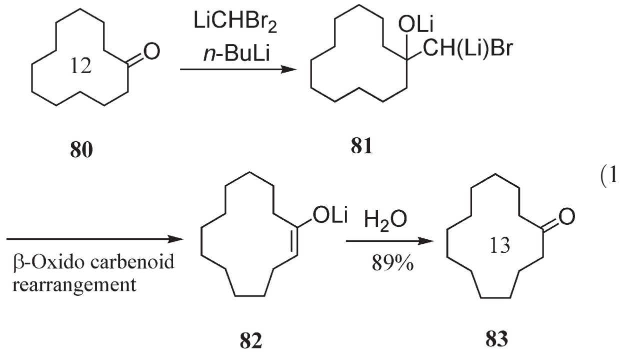
79 E= D (80%, D-content 98%), PhCHOH (64%), PhCO (54%), I (50%)

The reaction of magnesium alkylidene carbenoids with lithium thiolates gave tri-substituted alkenyl sulfides **79** in good yields through the alkenylmagnesium intermediates **78** (eqn (9)).[26] Thus, magnesium alkylidene carbenoid **53** was generated in toluene at −78 °C and to this solution was added lithium thiolate of *p*-toluenethiol (3 equiv.) to give alkenylsulfide **79** (E = H) in 80% yield. In this reaction, the presence of 1,2-dimethoxyethane (DME) as an additive was found to be effective. In addition, it was found that the reaction with arenethiolates gave better yields compared with the reaction with alkanethiolates.

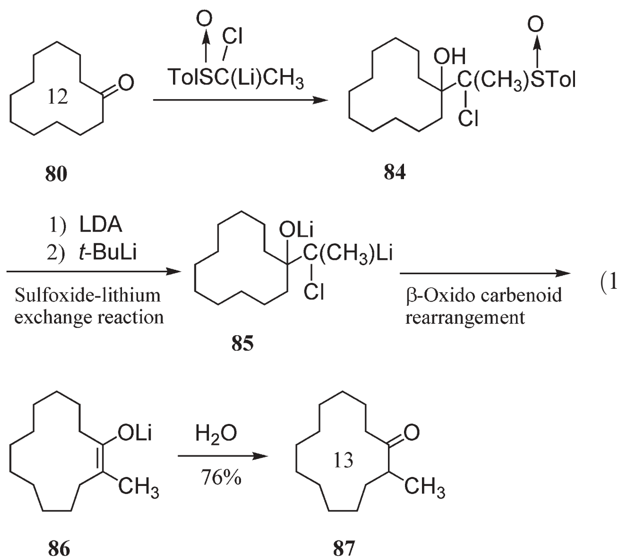
Trapping of the alkenylmagnesium intermediate **78** with several electrophiles was found to be possible to give the alkenylsulfides having a tri-substituted alkene **79**. Thus, the reaction was quenched with D_2O to afford the deuterated vinyl sulfide **79** (E = D) in 80% yield with 98% deuterium content. The reaction with aldehydes, benzoyl chloride, and iodine gave moderate to good yields of the desired alkenylsulfides **79**. The development of new synthetic methods with aryl 1-chlorovinyl sulfoxides including the chemistries of the magnesium alkylidene carbenoids has been reviewed by the author.[27]

5 Magnesium β-oxido carbenoids

Homologation of carbonyl compounds from lower carbonyl compounds by carbon–carbon coupling is an important and extensively used method for preparation of the desired carbonyl compounds.[28] One-carbon ring-expansion[29] or one-carbon homologation of ketones or aldehydes *via* a β-oxido carbenoid is one example of the homologation and a few methods have been reported.[30,31] For example, as shown in eqn (10), Taguchi and Nozaki reported in 1974 a one-carbon ring enlargement of cyclododecanone **80** to cyclotridecanone **83** with dibromomethyllithium through β-oxido carbenoid **81**.[30a,30c] This reaction was expected to proceed *via* a one-carbon expanded enolate **82**. Cohen and co-workers used bis(phenylthio)methyllithium as a source for the β-oxido carbenoid.[31]



(10)

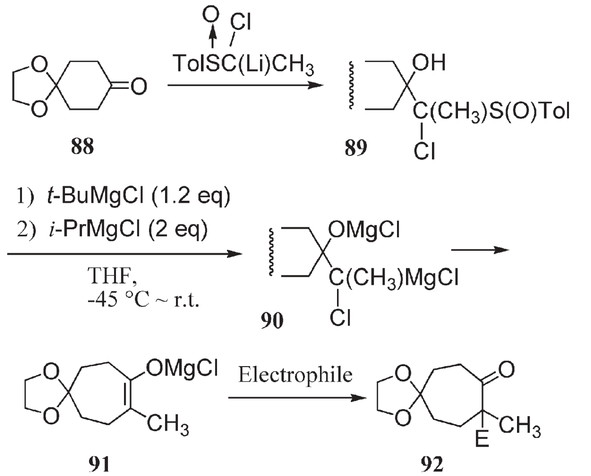


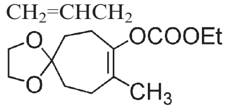
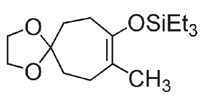
(11)

The author's group used lithium α-sulfinyl carbanion of 1-chloroalkyl aryl sulfoxides as the source for the β-oxido carbenoids (eqn (11)).[32] Thus, treatment of lithium α-sulfinyl carbanion of 1-chloroethyl *p*-tolyl sulfoxide with cyclododecanone **80** gave adduct **84** in high yield. The adduct was treated with LDA (lithium alkoxide was formed) followed by *tert*-butyllithium to give β-oxido carbenoid **85** by the sulfoxide–lithium exchange reaction. The β-oxido carbenoid rearrangement then takes place to afford one-carbon expanded enolate **86**, which was finally treated with water to give a one-carbon homologated cyclotridecanone having a methyl group at the α-position **87** in 76% yield.

The author's group further investigated this reaction and found that in some cases magnesium β-oxido carbenoids gave better results. Trapping of the enolate intermediates with several electrophiles was successfully carried out and a new method for a synthesis of one-carbon expanded cyclic α,α-disubstituted ketones from lower cyclic ketones was realized. An example using 1,4-cyclohexanedione mono ethylene ketal **88** as a representative cyclic ketone is shown in Table 5.[33b]

Table 5 Synthesis of 2-methyl-2-(substituted)cycloheptanones **92** from cyclohexanone derivative **88**, 1-chloroethyl *p*-tolyl sulfoxide, and electrophiles



	92	
Electrophile	E	Yield%
CD_3OD	D	75[a]
CH_3CH_2CHO	CH_3CH_2CHOH	71
PhCHO	PhCHOH	64
PhCOCl	PhCO	63
CH_3I	CH_3	73[b]
$PhCH_2Br$	$PhCH_2$	75[b]
$CH_2{=}CHCH_2I$	$CH_2{=}CHCH_2$	59[b]
ClCOOEt		74
Et_3SiCl		75[b]

[a] Deuterium content 95%. [b] HMPA was added as an addictive.

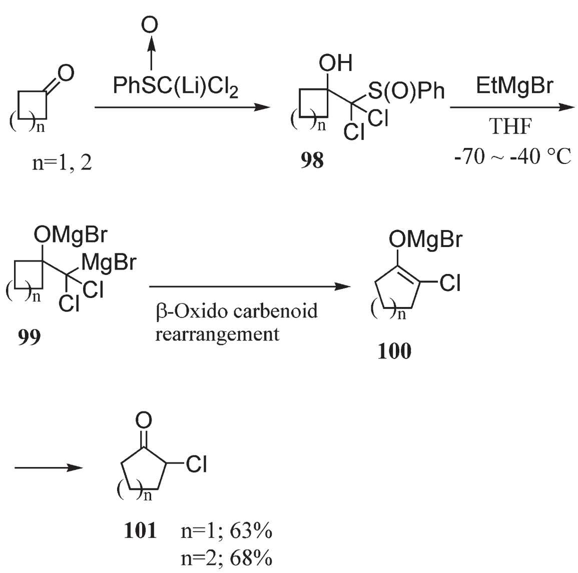
Thus, lithium α-sulfinyl carbanion of 1-chloroethyl *p*-tolyl sulfoxide was reacted with 1,4-cyclohexanedione mono ethylene ketal **88** to afford the adduct **89** in quantitative yield. The adduct was treated with *tert*-butylmagnesium chloride (magnesium alkoxide was formed) followed by isopropylmagnesium chloride to result in the formation of magnesium β-oxido carbenoid **90**. The β-oxido carbenoid rearrangement then takes place to give one-carbon expanded magnesium enolate **91**. Finally, an electrophile was added to the reaction mixture to give one-carbon expanded ketone having methyl and the group from the electrophile reacted at the α-position **92**.

Quenching of this reaction with deuterio methanol gave 2-methylcycloheptanone having deuterium at the 2-position (**92**; E = D) in 75% yield with 95% deuterium incorporation. Aldehydes and benzoyl chloride gave the desired products in 60–70% yields. Alkylation of the enolate intermediate **91** was successfully carried out with alkyl halides in the presence of HMPA in good yields. The reaction with ethyl chloroformate and chlorotriethylsilane gave enol carbonate and silyl enol ether in 74 and 75% yield, respectively. This chemistry was found to be applicable to large-membered cyclic ketones and aldehydes.[33]

Application of the method described above to unsymmetrical cyclic ketones, 2-substituted cyclohexanones, gave 2,7-disubstituted and 2,2,7-trisubstituted cycloheptanones (Scheme 9).[34] Treatment of lithium α-sulfinyl carbanion of 1-chloroethyl *p*-tolyl sulfoxide with 2-substituted cyclohexanones (**93a** and **93b**) afforded adducts as a mixture of two diastereomers. The main adducts were first treated with *t*-BuMgCl (formation of the magnesium alkoxides) followed by *i*-PrMgCl (4 equiv.) at 0 °C to room temperature to give the magnesium β-oxido carbenoid **94**. The β-oxido carbenoid rearrangement then took place to afford one-carbon ring-expanded magnesium enolates **95**. Quenching of this magnesium enolate with water afforded 2,7-disubstituted cycloheptanone derivatives **96a** and **96b** both in over 80% yields.

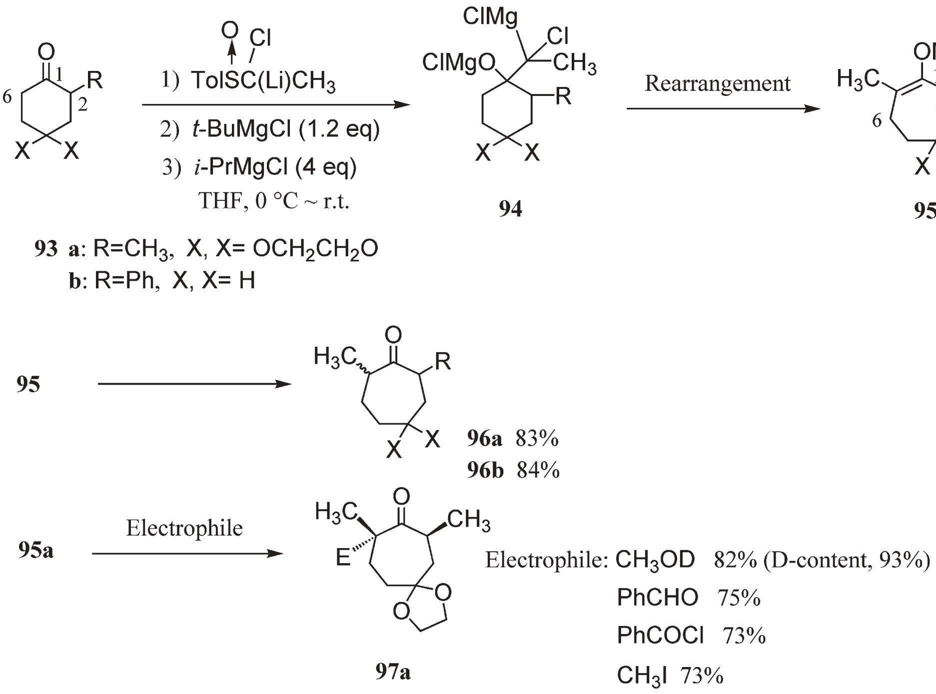
Very interestingly, from the structure of the product **96**, it was proved that the carbon–carbon insertion took place between the C_1 and C_6 carbons of the starting cyclohexanones **93**. The rearrangement is in the reverse direction to that usually reported in this type of reaction.[30] In addition, the magnesium enolate intermediate **95** could be trapped with several electrophiles, such as benzaldehyde, benzoyl chloride, and iodomethane to obtain 2,2,7-trisubstituted cycloheptanones **97a** in good yields. This method is very useful for the synthesis of 2,7-disubstituted cycloheptanones and 2,2,7-trisubstituted cycloheptanones from 2-substituted cyclohexanones with one-carbon ring-expansion in only two steps.

Using dichloromethyl phenyl sulfoxide in this procedure as a one-carbon homologating agent gave some results (eqn (12)).[35]



(12)

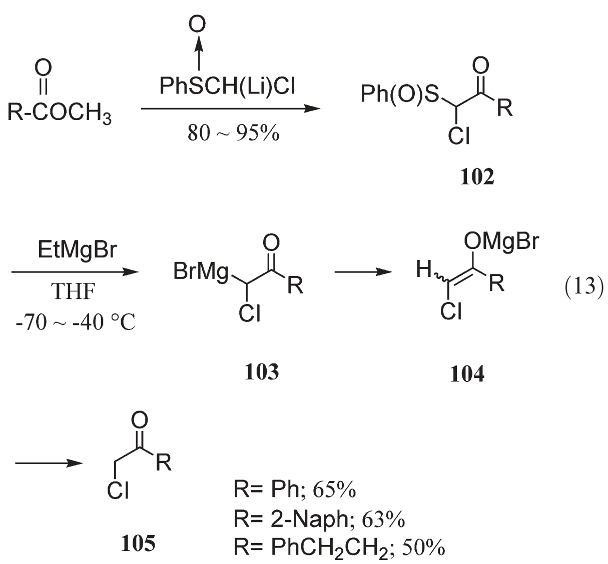
Thus, treatment of the lithium α-sulfinyl carbanion of dichloromethyl phenyl sulfoxide at −60 °C with cyclobutanone and cyclopentanone gave the adducts **98** in almost quantitative yields. The sulfoxide–magnesium exchange reaction of the adducts **98** with EtMgBr gave magnesium β-oxido carbenoids **99**. The β-oxido carbenoid rearrangement then took place to give one-carbon expanded magnesium enolate having a chlorine **100**, which was treated with water to afford α-chloroketone **101** with one-carbon homologation in moderate yield. Unfortunately, this method could not be applied in larger cycloalkanones and acyclic ketones. Application of this



Scheme 9

method to aldehydes gave chloromethyl aryl ketones and chloromethyl alkyl ketones in moderate yields.[35]

Finally, a magnesium carbenoid next to carbonyl carbon was reported (eqn (13)).[35] The lithium α-sulfinyl carbanion of chloromethyl phenyl sulfoxide was reacted with methyl esters to give α-chloro-α-sulfinylmethyl ketones **102** in 80–95% yields. Treatment of **102** with EtMgBr in THF at low temperature resulted in the formation of magnesium carbenoid **103**, and quenching of this reaction with water afforded α-chloroketones **105** in moderate yields. Obviously, the sulfoxide–magnesium exchange reaction of **102** proceeded to give magnesium carbenoid **103**; however, Wolff-type rearrangement does not take place, instead, magnesium enolates **104** were produced in this reaction.



6 Summary and outlook

As outlined, magnesium carbenoids are relatively stable compounds compared with the corresponding traditional lithium carbenoids. Therefore, we can manage the carbenoids in a similar way as the usual reactants with a little precaution. Generation of the magnesium carbenoids can be performed mainly in two ways, halogen–magnesium exchange and sulfoxide–magnesium exchange reactions at low temperature usually at −78 °C. As mentioned above, concerning the generation of the magnesium carbenoids, starting from sulfoxides having a halogen on the α-position using 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 of the magnesium carbenoids is far more interesting from the synthetic viewpoint as mentioned above.

The chemistry of the magnesium carbenoids started practically in the last ten years of the 20th century; in other words, it is a quite young chemistry. Many new and very interesting results will be forthcoming from this field.

Acknowledgements

The author thanks Professor Carsten Bolm, Institute fur Organische Chemie der RWTH Aachen, for his helpful discussion.

References

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