Magnesium in Methanol (Mg/MeOH) in Organic Syntheses

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Abstract: Magnesium in methanol(Mg/MeOH) system is an extremely versatile, efficient, economical and convenient reducing agent for various reactions useful for organic synthesis such as reductive cyclization, reductive elimination, reductive cleavage, reduction of a conjugated double bond, desulfonylation, and reduction of various functional groups. This comprehensive review is intended to highlight the use of Mg/MeOH in each of these organic transformations.

INTRODUCTION

Among electron transfer reactions using Mg metal, reactions in protic solvents have not been fully exploited in comparison with reactions in aprotic solvents such as Grignard reaction [1], pinacol coupling [2], and low valent transition metal complex reactions [3].

Utility of Mg/MeOH as an electron transfer reagent has appeared in literature rather sporadically since the ability of Mg/MeOH to reduce functional groups such as nitro, oxime, ketone and halogen was first discovered by Zechmeister in 1920s [4]. There, after its use has been expanded not only to the selective reduction of various functional groups, but also to the reduction of conjugated double and triple bonds tethered to diverse functional groups such as esters [5,8], nitriles [6], amides [7] and aromatics [8] to the corresponding saturated analogs and to the dehalogenation [9] of alkyl halides. A particular advantage of this method is the regioselective reduction of a conjugated double bond in the presence of a nonconjugated double bond. It was also superior for desulfonylation in its convenience and environmental benignancy to the most frequently employed conventional sodium amalgam in alcohol [10]. Another salient feature of this reagent is that C-C bond formation is possible *via* reductive cyclization [11]. Reductive cyclization has been known to employ electrochemistry [12] and photochemistry [13], or employing reagents *viz*. SmI_2 [14] or Bu_3SnH [15]. Although efficient methodologies are available for annulations, the search for better and more convenient methods continues [16]. Another striking feature of Mg/MeOH is the reductive cleavage of the C-O bond tethered to the γ-position of α,β-unsaturated esters and halomethyls [17] and of the C-N bond of aziridine [18]. The scope and limitation of these reactions by Mg/MeOH are quite similar to that of SmI_2, which were thoroughly reviewed by Molander, *et al*. [19].

Its merit should be emphasized in its economy, versatility, environmental benignancy and handling, compared to its equivalent metal reagent [20].

Reductive Cyclization

Radical cyclizations *via* the intramolecular addition of carbon radical to multiple bond have been extensively demonstrated as useful tools in organic synthesis [21]. Among these, intramolecular ketyl-olefin cyclizations are relatively new and have many advantages, compared to simple radical cyclizations [22]; particularly high diastereoselectivity at the newly formed carbon-carbon bond of the cyclic product. In order to achieve intramolecular ketyl-olefin cyclizations, methods to create ketyl radical *via* electrochemical [23], photochemical [24], and low valent metals [25] have been employed. Sm(Π) [26] and organotin [15] in aprotic solvent have been extensively exploited for ketyl-olefin cyclization relative to other low valent metals. However, both reagents are known to have drawbacks in its economy and convenience [22(d)]. In an effort to overcome these drawbacks and expand its utility, Mg/MeOH has been demonstrated as a convenient single electron transfer reagent for a number of reductive reactions [27]. In contrast to abundant examples of Sm(Π) or organotin mediated ketyl-olefin cyclization reactions, precedents of magnesium induced intramolecular cyclization *via* unequivocal addition of ketyl radical to multiple bond were not found before the examples of reductive cyclization of ketones tethered to activated olefin [28].

The cyclization reaction of ketones tethered to α,β-unsaturated esters proceeded smoothly when the substrates were treated with 3 equiv. of magnesium in dry methanol in the presence of a catalytic amount of $HgCl_2$ at -23°C for 3h (Scheme **1**). The cyclization gave mixtures of *trans* and *cis* isomers in excellent yields along with trace amounts of simple reduction products. In all cases, *trans* isomers were predominant, and all *cis* products lactonized under the reaction conditions. Regardless of the configuration of the double bond, identical product yields and isomer ratios were obtained. This result is in sharp contrast to the previous stereochemical results of ketyl additions to α,β-unsaturated ester groups, in which the geometry of the double bond plays a critical role in determining the stereoselectivity [29, 30].

In order to explain both the identical product isomer ratios for both substrate geometries and the failure to isolate the equilibrium mixture of the substrate, a plausible mechanistic pathway was illustrated (Scheme **2**).

The rapid equilibrium might occur at either the stage of the allylic radical (stage I) or the allylic anion (stage II). Since it is well known that the attack of a carbon-centered radical on a carbonyl group is an energetically unfavorable process [31] and, the resulting alkoxide radical easily undergoes β-fragmentation [32], it must be the allylic anion rather than the allylic radical that attacks the carbonyl group. It is reasonable to assume that by the means of rapid

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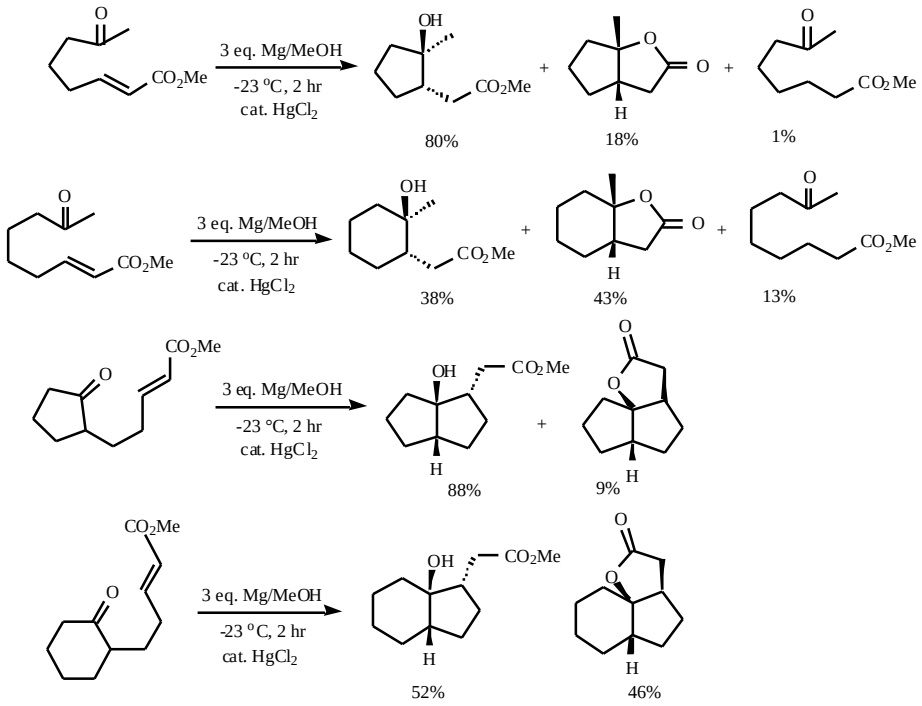
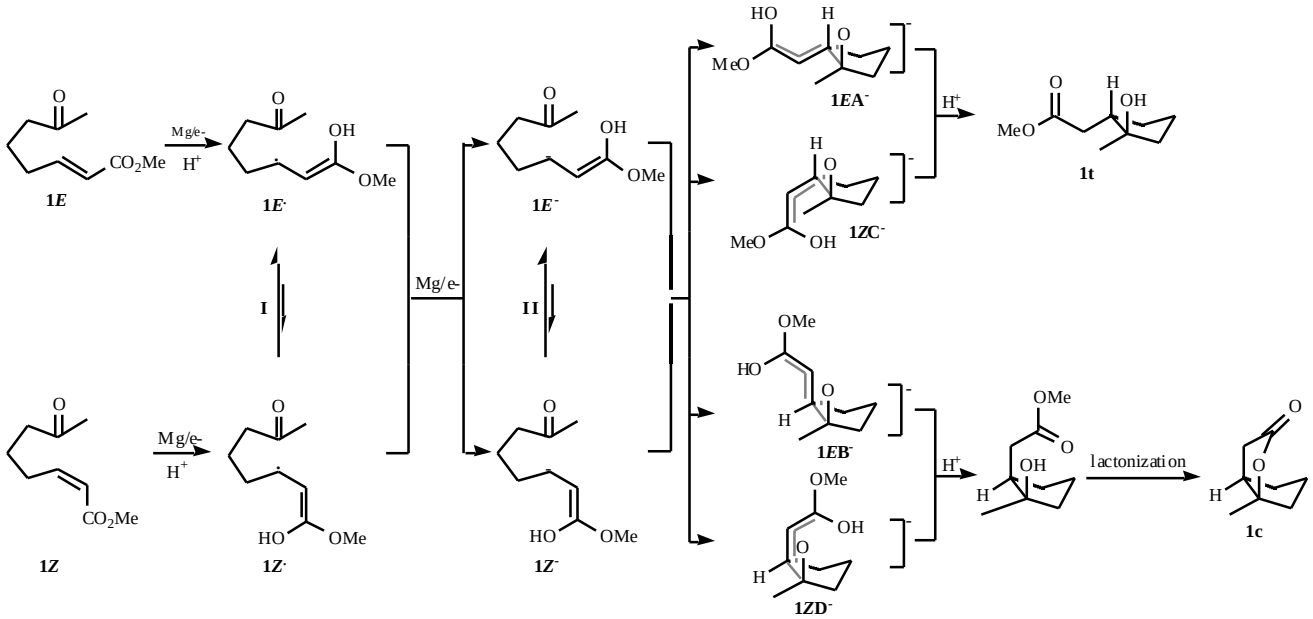


Scheme 1.



1*EA*$^-$; electronically favorable & sterically unfavorable

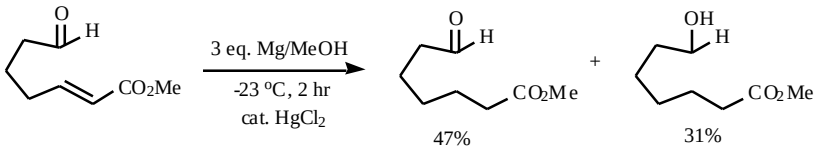
1*EB*$^-$; electronically unfavorable & sterically favorable

1*ZC*$^-$; electronically favorable & sterically unfavorable

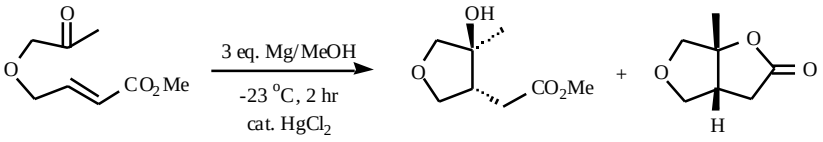
1*ZD*$^-$; electronically unfavorable & sterically favorable

Scheme 2.

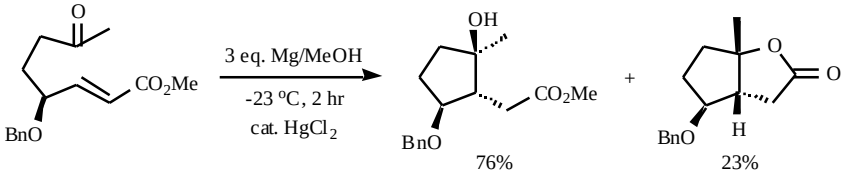
equlilbria of geometrically isomeric allylic radicals **1*E***$^·$ and **1*Z***$^·$ and/or allylic anions **1*E***$^-$ and **1*Z***$^-$ formed from either isomers of **1**, the sterically more favorable E allylic anion **1*E***$^-$ would be the predominant species. These equilibria would lead to a mixture of the four possible transition state structures (**1*EA*, 1*EB*, 1*ZC*,** and **1*ZD***) illustrated (Scheme **2**). Transition states **1*EA*** and **1*ZC***, derived from *E* and *Z* allylic anions **1*E***$^-$ and **1*Z***$^-$, respectively, would lead to a *trans* product, whereas transition states **1*EB*** and **1*ZD***, form **1*E***$^-$ and **1*Z***$^-$, would form a *cis* product, which eventually lactonizes under the reaction conditions. It is highly probable that, since the electronic repulsion between the C=O electron and the axial anion moiety C_β-C_α-C-O outweighs the nonbonded steric interaction between the CH_3 of acyl group and the C_α-C_β bond, transition states **1*EA*** and **1*ZC*** would be preferred relative to transition states **1*EB*** and **1*ZD*** [30(a)]. Because of the identical results obtained from *E* and *Z* isomers, it can be deduced that each isomer is converted to the same equilibrium mixture and that the favorable configuration of the allylic anion must be the thermodynamically favorable E form, formed through the fast rotation of the C_α- C_β bond of the α,β-unsaturated ester.



Scheme 3.



Scheme 4.



Scheme 5.

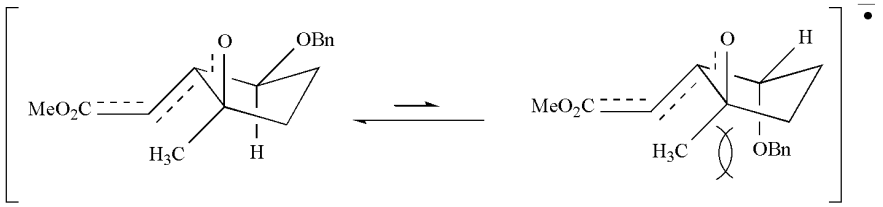
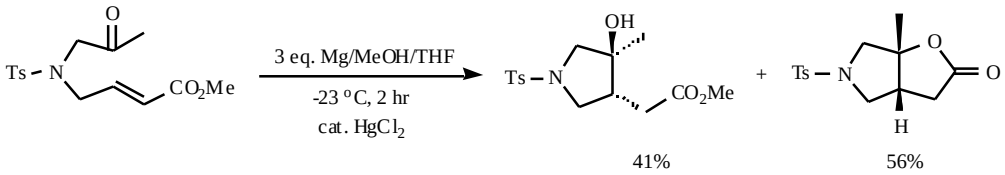


Fig. (1).



Scheme 6.

Instead of the expected cyclized products, aldehydes provided two kinds of saturated, alicyclic reduction products: (1) the product of simple reduction of the olefinic double bond and (2) the fully reduced saturated alcohol (Scheme **3**). It seems that the equilibrium between the free aldehyde and a hemiacetal in methanol solvent prohibits cyclization [33]. Thus, the olefinic double bond of the predominant hemiacetal species was reduced to give the corresponding saturated aldehyde after workup; after reduction of the olefinic double bond of the free aldehyde form, the aldehyde group was further reduced to afford the corresponding saturated alcohol.

The low yield of cyclized products (13%) from oxa ketone is attributed to the facile cleavage of the C_4-O bond (Scheme **4**). This cleavage produces methyl 3-butenoate as the major product. Cleavage of the alkoxy group indicates that carbanionic rather than radical character must have developed at the β–carbon.

In contrast, 4-(benzyloxy) ketone gave a mixture of cyclized products of *cis* and *trans* isomers in quantitative yield without any trace of cleavage product (Scheme **5**).

The dramatic change in the amount of β-cleavage between these two compounds which both have an alkoxy group at the same γ –position, must be due to the fact that, in the transition state of cyclization the carbanion lobe of substrate (Scheme **4**) is aligned with the C-O bond in the *syn*-periplanar position in such a way that severe electrostatic repulsion between the nonbonding electrons on the oxygen atom and the carbanion causes these two groups to swing into the *anti*-periplanar position, which, in turn, makes an E2-type elimination occur easily. In contrast, the benzyloxy group of substrate (Scheme **5**) is at a 120° angle with respect to the carbanion lobe in the transition state, and this dihedral angle is unfavorable for E2-type elimination. The *trans* relationships between the (carbomethoxy)methyl appendage and the benzyloxy group of products must stem from the most favorable transition state, wherein the bulky benzyloxy group is aligned in an equatorial position (Fig. (**1**)).

5-Aza ketone provided cyclized products in high yield (97%) but with poor stereoselectivity. In this case, dry THF was used as a cosolvent due to poor solubility of the substrate in dry methanol (Scheme **6**).

It seems that a stereoelectronic interaction between the carbonyl oxygen atom and the nonbonding electron pair on nitrogen had an influence on the transition state (Fig. (**2**)).

Under the same reaction conditions, keto nitrile gave 42% of a cyclized product mixture, 29% of the product of reduction of the olefinic double bond, and 27% of the

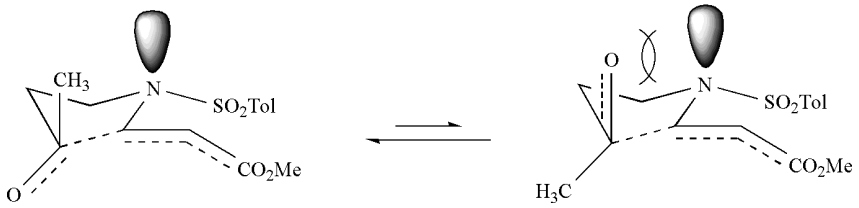
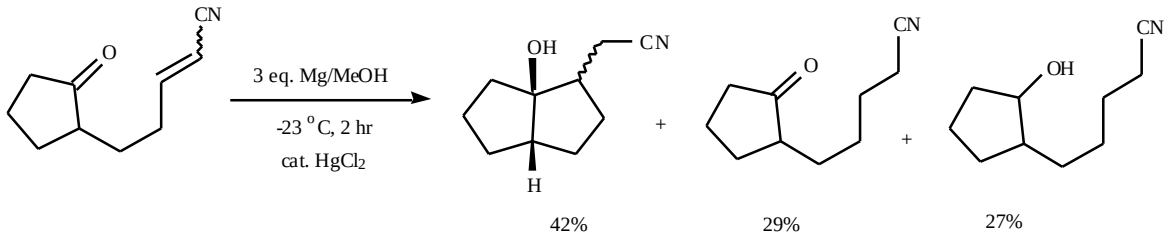
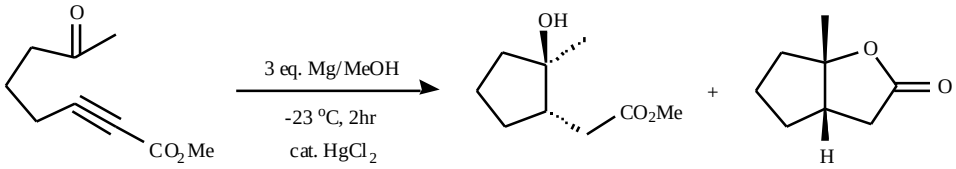


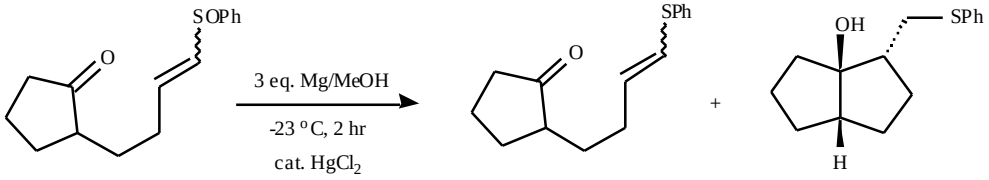
Fig. (2).



Scheme 7.



Scheme 8.



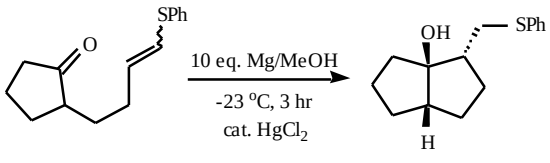
Scheme 9.

corresponding saturated cyclopentanol (Scheme **7**). The product mixture indicates that protonation and cyclization of the carbanion species occurred competitively. Consequently, about half of the double bond reduction product was further reduced, probably *via* a ketyl intermediate, with residual Mg. The possibility of ketyl formation before the reduction of the α,β-unsaturated nitrile group was excluded since cyclopentanol with an α,β-unsaturated nitrile group was not detected. According to the results reported by Hudlicky *et al*., it is highly unlikely that an isolated carbonyl group would be reduced prior to an α,β-unsaturated nitrile group [34].

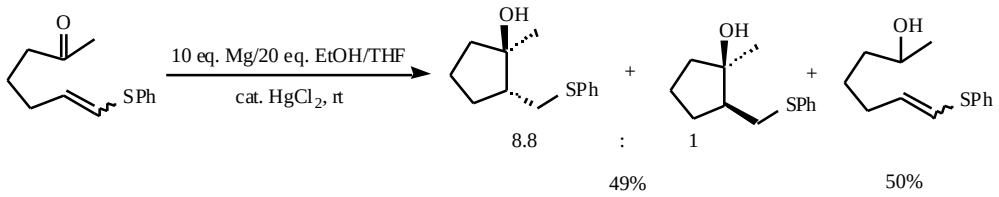
Since the cyclization of acetylenic ketone resulted in the same product ratio as that of olefinic ketone (Scheme **8**), it might be cyclization that occurs after the reduction of the triple bond to a double bond *via* the same intermediate as in the case of olefinic ketone (Scheme **1**) [35].

When keto α,β-unsaturated sulfoxide was used as an eletron acceptor only a small amount of the expected cyclized product was formed. Surprisingly, keto sulfoxide (*Z* and *E*) underwent mostly deoxygenation to give the corresponding sulfide (*Z* and *E*) in 85% yield along with cyclized sulfide in 9% yield (Scheme **9**). Deoxygenations of isomeric keto sulfoxides *E* or *Z* proceeded without isomerization of the olefinic double bond so that each of the isomeric keto sulfoxides gave a deoxygenated product retaining its original double bond configuration (*E* or *Z*, respectively). Similar deoxygenation of 1-alkenyl sulfoxides with ethylmagnesium bromide/cuprous iodide has been reported by Posner *et al*. [36]. The double-bond geometry of substrate did not affect the diastereoselectivity so that the same cyclized product was obtained. This result contrasts with that of the SmI_2-mediated cyclization where a dramatic change in diastereoselectivity was observed depending on the substrate geometry [30(a)]. The yield of cyclized sulfide increased remarkably at the expense of deoxygenated product as the amount of magnesium metal and the reaction time increased [30(a)].

Reaction of α,β-unsaturated sulfides *E* and *Z* with 10 equiv of Mg afforded cyclized sulfide in 97% and 91% yields, respectively (Scheme **10**). It is obvious that the cyclization occurs *via* keto sulfide rather than by direct reductive cyclization of sulfoxide.

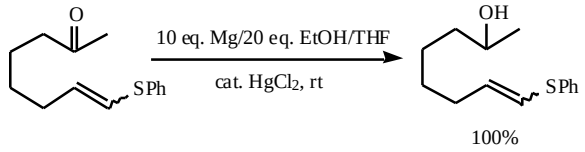


Scheme 10.



Scheme 11.

Consequently, by controlling the amount of magnesium metal added, either deoxygenation or cyclization of sulfoxides was performed conveniently under mild conditions [27(b)]. Simple 1-alkenyl phenyl sulfide was inert to the same reaction conditions, even with excess magnesium in the presence of mercuric chloride [37]. This result reveals that an electron is transferred from magnesium metal to the carbonyl group rather than to the phenyl vinyl sulfide group. The mechanism is similar to that of the SmI_2-mediated cyclization of ketones tethered to activated olefins and to the pinacol-type reaction of carbonyl compounds [38].



Scheme 12.

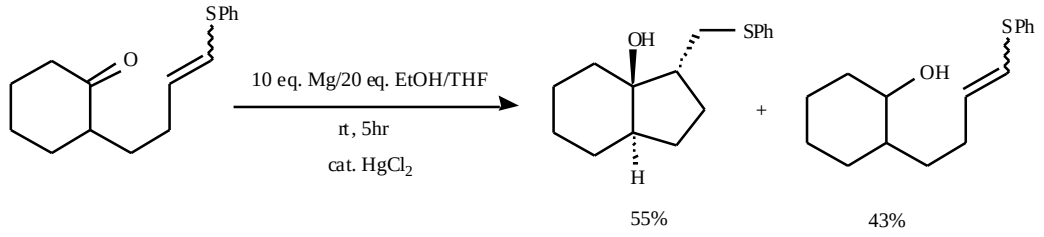
Under modified conditions (10 equiv Mg, 20 equiv EtOH in THF, cat $HgCl_2$, room temperature) where EtOH was used as a proton source in THF solvent, linear aliphatic ketone afforded isomeric cyclopentanols as a mixture of *trans* and *cis* in 49% yield (*trans*/*cis*= 8.8/1) along with simply reduced alcohol in 50% yield (Scheme **11**). Interestingly, ε-alkenyl ketone gave only the simply reduced alcohol quantitatively without any trace of cyclized product (Scheme **12**). It seems that reduction of carbonyl group is more favorable than *6-exo-trig* cyclization reaction.

Cyclohexanone gave a single diastereomer in 55% yield along with a simply reduced alcohol in 43% yield (Scheme **13**). It is interesting to note that a similar substrate without phenylthio group does not cyclize with SmI_2 [39].

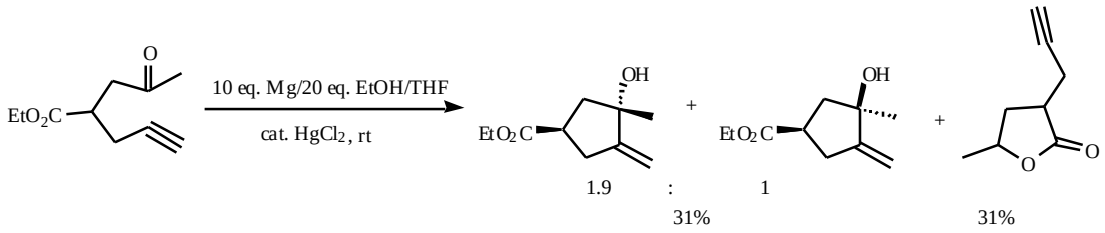
δ-Alkynyl ketone afforded a product mixture consisting of the expected allylic alcohol as a mixture of *trans* and *cis* isomer(31%, *trans*/*cis* = 1.9/1) and γ-butyrolactone (31%) resulting from lactonization of the corresponding alcohol formed by simple reduction of carbonyl group and unreacted starting material (18%) (Scheme **14**).

δ-Alkenyl ketone provided product as a single diastereoisomer in 70% yields (Scheme **15**). The same kind of high diastereoselective cyclization was also achieved with SmI_2 in 75% yield [39]. The reaction seems to go through the same kind of chelated transition structure as in the SmI_2-mediated reaction. A mixture of geometric isomers (*Z*/*E*; 1/1) of 2-phenylthioalkenyl ketone gave the cyclized product in 93% yield with high diastereoselectivity (*trans*/*cis* = 17/1) (Scheme **16**) [29]. Strikingly, the cyclic adduct was not obtained at all with the SmI_2 [40].

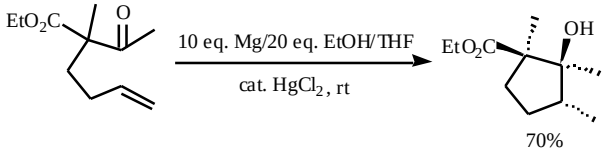
Three transition states can be postulated to explain *cis* relationship between OH and CO_2Et of the product from β-keto esters shown as below (Fig **3**)) [39]. Transition state **A** and **B** is more favorable than that of **C** because **C**, cannot attain the correct orbital alignment without significant distortion and ensuing strain. The stability of **A** is reinforced



Scheme 13.

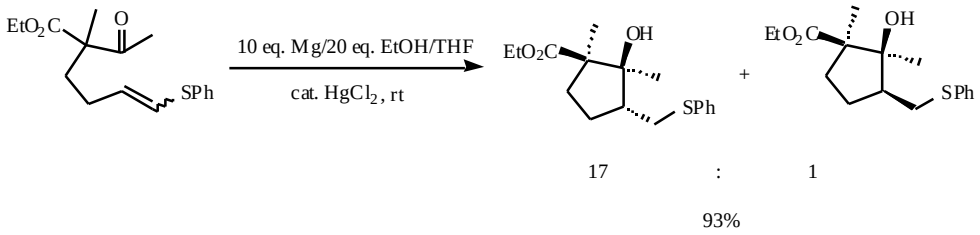


Scheme 14.



Scheme 15.

by steric interactions directing the developing methylene center away from the face of the molecule with the large chelated ring and by the electronic repulsion between the oxygen atom of the nucleophilic ketyl and the vinyl appendage.



Scheme 16.

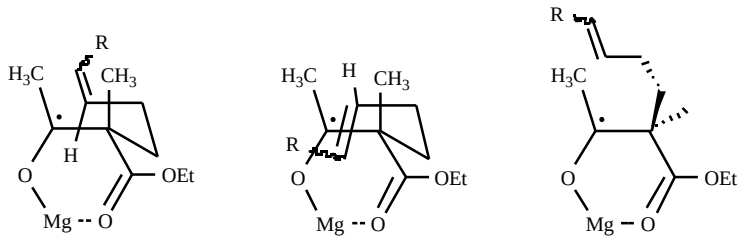
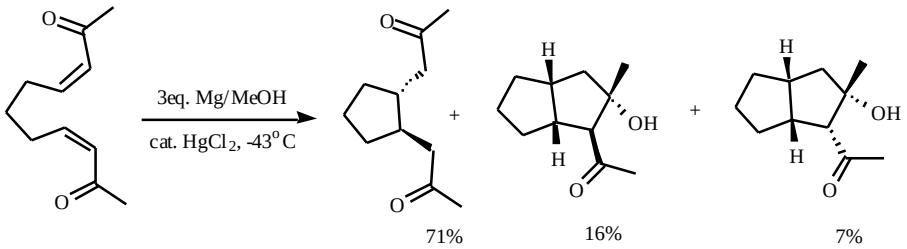
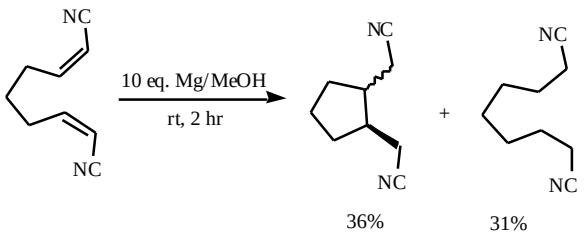


Fig. (3).



Scheme 17.

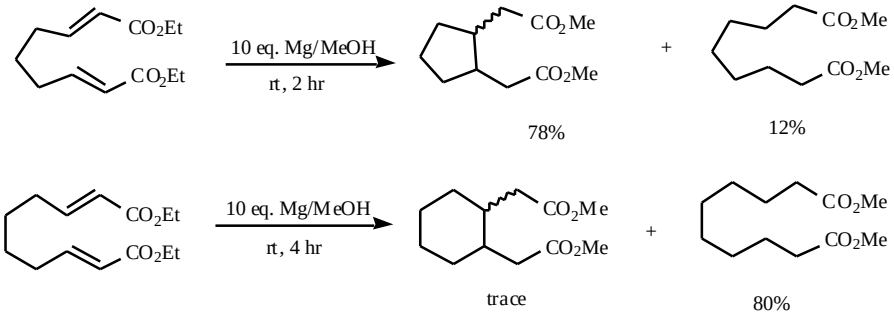


Scheme 18.

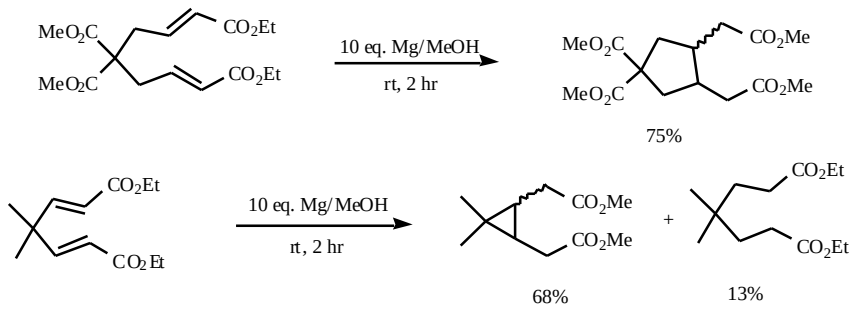
Reductive cyclization with Mg/MeOH was further demonstrated with substrates containing bis–activated double bond conjugated with ketone, nitrile or ester (Scheme **17**-**19**) [28]. The substrate was designed to use the first activated double bond as an electron acceptor and the second one as a subsequent trap of a radical anion to form intramolecular C-C bond formation. It has been reported that the electrochemical hydrodimerization of α,β-unsaturated ketones, esters, and nitriles proceeds *via* anion radicals in aprotic media and in the absence of metal cations, and allyl radicals in protic media, respectively [41]. Methods for intramolecular β-coupling reaction of activated olefins have been limited to electrochemical hydrodimerization and n-Bu_3SnH [15].

Geometric isomers of bisolefins activated with a ketone group provided *trans* product and cyclized products resulting from the *cis* product presumably *via* 1,4-addition of allyl radical intermediate was obtained in 94% yield [28].

Regardless of the configuration of the carbon-carbon double bond, *trans*-product was obtained as a major product not only in conjugated ketone but also in conjugated esters and nitriles [42]. It might be mostly due to steric hindrance caused by a vicinal appendage in the course of cyclopentane ring formation [28]. Comparison of substrates differing in their electron withdrawing groups *viz*. dienone, diester, and dicyano reveals that the presence of the most electron withdrawing *viz*. dicyano leads to the formation of reduced product to a greater extent whereas dienone did not give any double bond saturated products [28].

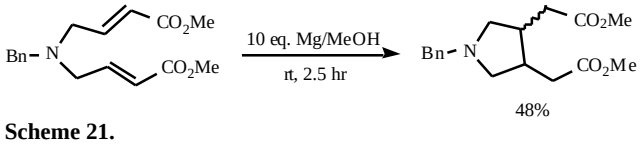


Scheme 19.

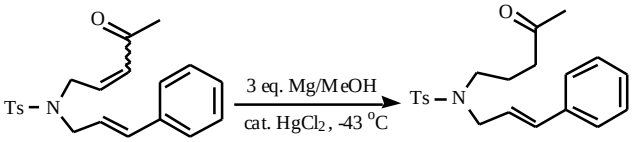


Scheme 20.

Gem-dialkyl effect was operative where reaction gave only cyclized product and no trace of reduced product could be obtained. When it comes down to cyclopropyl ring formation, a significant amount of simple reduction product was obtained (Scheme **20**).



Scheme 21.



Scheme 22.

It is interesting to note that amine with bis conjugated ester group furnished cyclized product (Scheme **21**) [42] whereas sulfonamide with enone and styryl group provided only reduced product (Scheme **22**) [28]. Although cyclization with conjugated ester tethered to ketone provided 6 *exo-trig* product as a major product (Scheme **6**), bis-activated olefin did not undergo annulation (only trace) to obtain only reduction product (Scheme **22**). It seems that the trapping of a generated radical anion is highly dependent on the character of the second conjugated double bond to be able to accept electron.

Reductive Cleavage

Reductive cleavage with Mg/MeOH was observed for the first time by Kandil *et al*. in the course of the synthesis of aggregation pheramone (+)-lineatin [43]. Unexpected reductive cleavage of the dioxolanyl group was noticed in an attempt to reduce the olefinic double bond of an α,β-unsaturated nitrile. Presumably reductive cleavage first gave β,γ-unsaturated nirile, which was subsequently isomerized into α,β-unsaturated nitrile after having been catalyzed with $Mg(OMe)_2$. Then the conjugated double bond was further reduced to afford the saturated product (Scheme **23**).

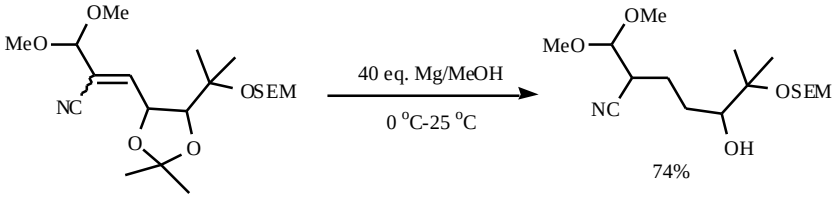
Extensive studies of reductive cleavage of various types of C-O and C-N bonds tethered to α,β-unsaturated esters and halomethyls provided a facile method for the synthesis of δ-hydroxy or δ-amino β,γ-unsaturated esters and allylic alcohols [17, 44].

Epoxy esters afforded the corresponding allylic alcohols as *E* isomers, exclusively (Scheme **24**).

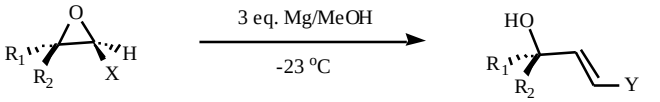
Similarly, dioxolanyl esters afforded the *E* isomers as the sole product, regardless of the original substrate stereochemistry (Scheme **25**).

Conformational equilibrium before the formation of a double bond was suggested as an explanation for the exclusive formation of *E* isomer (Fig. (**4**)). Steric hindrance exerted by the epoxy or dioxolanyl group on the conformation of the radical anion must play a major role during the formation of the new olefinic bond, and thus controls the stereochemistry of the product (Fig. (**4**)). Steric effects from R_2 on the conformational equilibrium are negligible, since the dioxolanyl compound (R_1, R_2 = H), as a mixture of *E/Z* isomers, also provided a single *E* isomer.

Regardless of substrate stereochemistry, all four isomers of epoxy esters provided the identical *E* isomer as noted previously with SmI_2 [6(k)]. Similarly, each of the four optically active stereoisomers of dioxolanyl esters resulted in the same optically active *E* isomer (Fig. (**5**)).

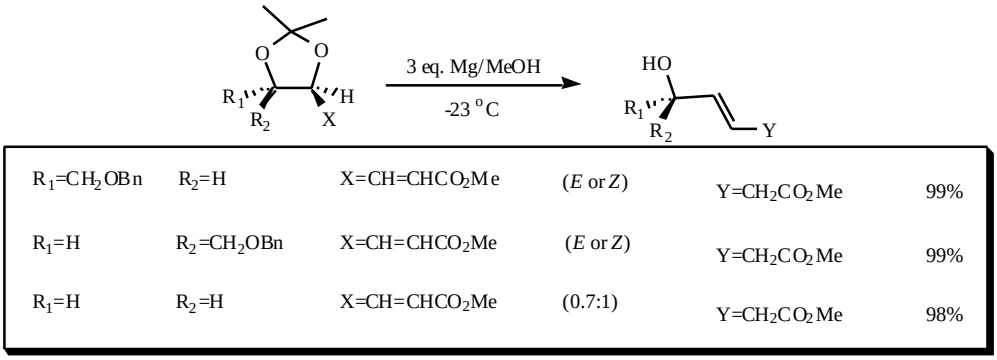


Scheme 23.



R_1=CH_2OBn	R_2=H	X=CH=$CHCO_2Me$	(*E* or *Z*)	Y=CH_2CO_2Me	98%
R_1=H	R_2=CH_2OBn	X=CH=$CHCO_2Me$	(*E* or *Z*)	Y=CH_2CO_2Me	98%

Scheme 24.



Scheme 25.

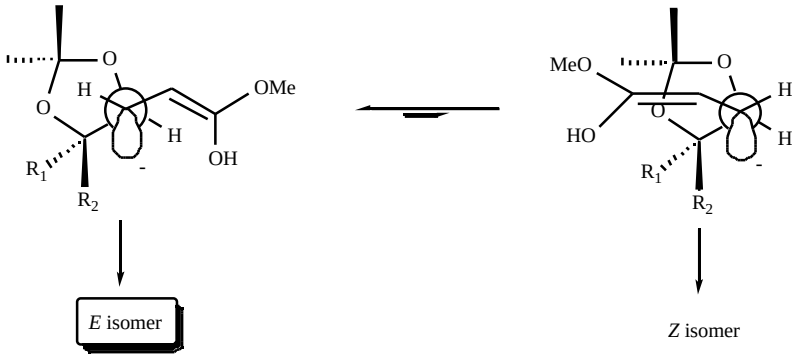


Fig. (4).

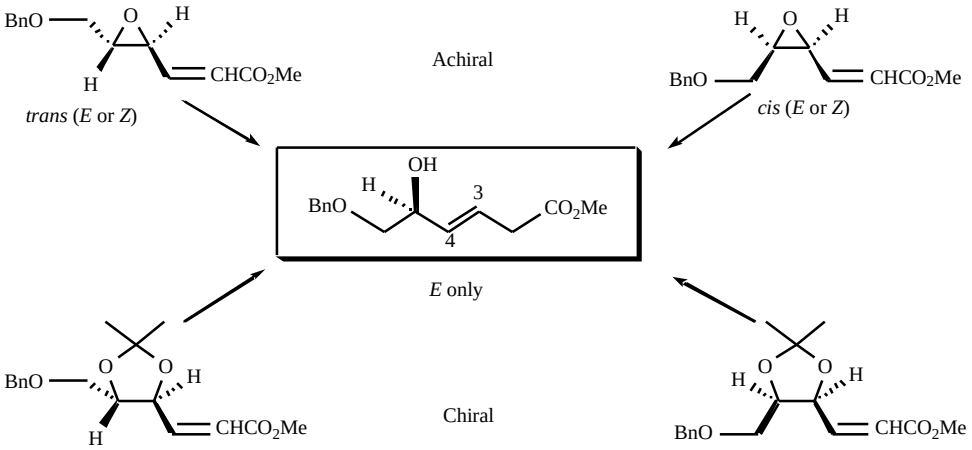
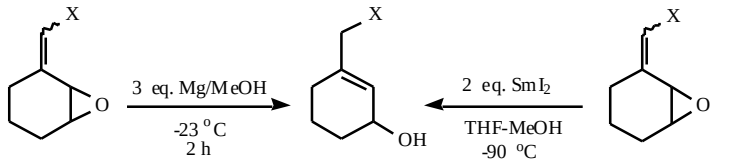


Fig. (5).

Reductive cleavage of cyclic epoxy esters previously performed with SmI_2 [6(k)] was compared with Mg/MeOH resulting in superior product yield. Under a more controlled reaction condition susceptible groups such as phenyl sulfonyl and phenylsulfoxide group were survived to give moderate yield of cleavage product (Scheme **26**).

The reductive cleavage of cyclic ether linkages in halofuranose and halopyranose derivatives was previously achieved using Zn/Ag graphite [45], Zn/alcohol [46], or Zn/AcOH [47]. Instead of halofuranose or halopyranose, cyclic ether linkages of tetrahydrofuran and tetrahydropyran substituted with α,β-usaturated ester group were cleaved (Scheme **27**-**29**) [17, 46].

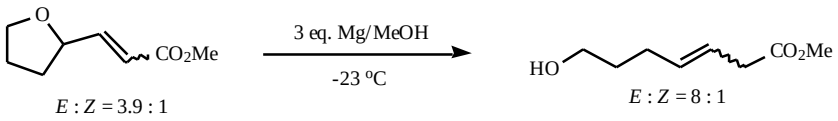
In contrast to the tetrahydrofuran ring where cleavage reaction gave the corresponding alcohol in almost quantitative yield (Scheme **27**), tetrahydropyran ring afforded a mixture of cleavage product (46%) and double bond reduction product without ring opening (51%) (Scheme **28**). Relative ring strain of tetrahydrofuran and tetrahydropyran must have played a major role during the cleavage of the C-O bond. By comparing the cyclic moiety of tetrahydrofuran with diemthyldioxolan, the methyl groups of diemthyldioxolan moiety, which is *syn* to the β,γ-unsaturated ester group, must have forced the equilibrium to shift to the more favorable conformer (*E* isomer) (Fig. (**4**)). Lack of the methyl group in the tetrahydrofuranyl moiety has led to a



X; CO_2Me	98 % (68 %)*	X; CO_2Et
CN	98 % (71 %)*	CN
SO_2Ph	61 %**	
SOPh	83 %**	

* Yield in parenthesis is by SmI_2. **3 eq. Mg/MeOH, cat. $HgCl_2$, -43 °C, 2hr.

Scheme 26.

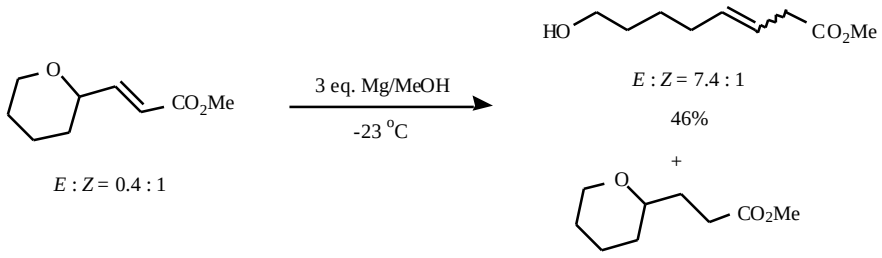


E : *Z* = 3.9 : 1

E : *Z* = 8 : 1

97%

Scheme 27.



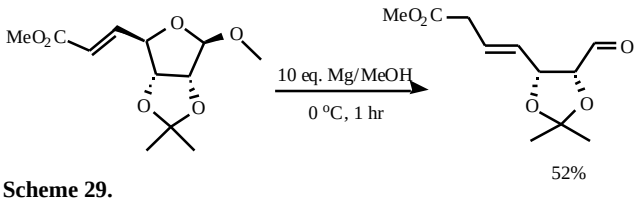
E : *Z* = 7.4 : 1

46%

E : *Z* = 0.4 : 1

51%

Scheme 28.



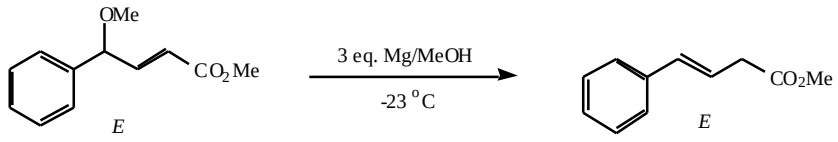
52%

Scheme 29.

significant loss of stereoselectivity, resulting in the formation of a significant amount of *Z* isomer (11%) (Scheme **27**). Even when the pure *E* isomer was used instead of 3.9:1 *E/Z* mixture, the same loss of stereoselectivity was observed.

In the same manner, strict stereocontrol was observed for γ-methoxy α,β-unsaturated ester (Scheme **30**), but was lost for γ-acetoxy α,β-unsaturated ester (Scheme **31**). Thus, pure *E* isomer of methyl ether gave alkene as a single *E* isomer, but acetate as a mixture of isomers (*E*/*Z*=3.4/1) gave product as a mixture of isomers (*E*/*Z* = 3.8/1).

Reductive elimination of the nitro group of γ-nitro-α,β-unsaturated esters was reported [48]. Although poor yields were obtained with various to γ-nitro-α,β-unsaturated esters, expected products of β-elimination were obtained (Scheme **32**).

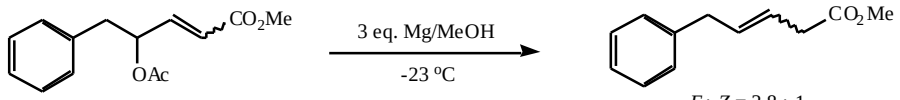


E

E

98%

Scheme 30.

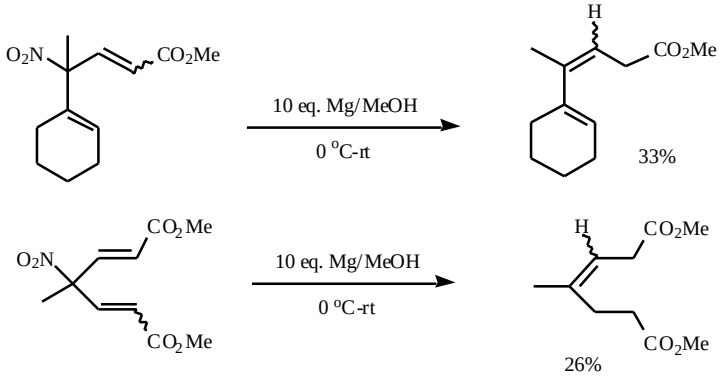


E : *Z* = 3.4 : 1

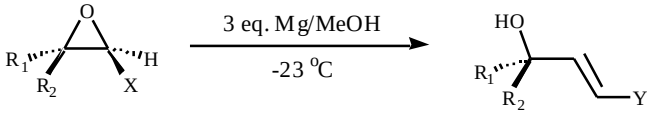
E : *Z* = 3.8 : 1

96%

Scheme 31.

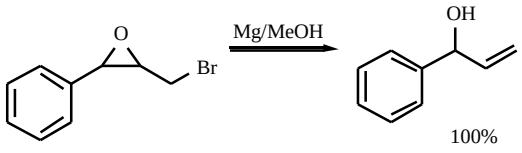


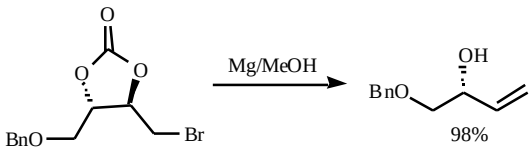
Scheme 32.



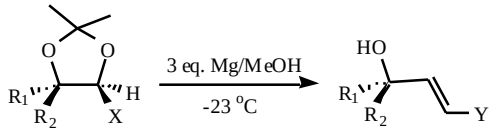
R_1=H	R_2=CH_2OBn	X=CH_2Cl	Y=H	no reaction
R_1=H	R_2=CH_2OBn	X=CH_2Br	Y=H	98%
R_1=H	R_2=CH_2OBn	X=CH_2I	Y=H	98%

Scheme 33.





Scheme 34.



R_1=CH_2OBn	R_2=H	X=CH_2Cl	Y=H	no reaction
R_1=CH_2OBn	R_2=H	X=CH_2Br	Y=H	99%
R_1=CH_2OBn	R_2=H	X=CH_2I	Y=H	99%

Scheme 35.

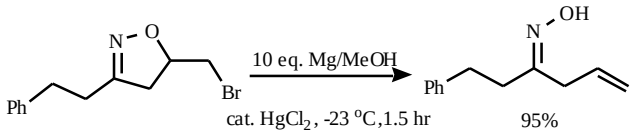
In the case of epoxy halomethyls, cleavage of the epoxides was facile for the bromide and iodide to give olefin, but chlorides were inert and did not yield a terminal allylic alcohol (Scheme **33**). The preferential reactivity of the halides (I>Br>Cl) toward Mg/MeOH has been reported previously [11].

Exclusive formation of allylic alcohol from epoxy halomethyls instead of vinyl ether stemming from radical cleavage of the C-C bond strongly suggests that Mg/MeOH produces carbanions which then undergo a cleavage reaction (Scheme **34**). Similar reductive cleavage of epoxy halomethyls to allylic alcohols by the use of Zn(Cu) couple under sonochemical conditions was reported [8(a)]. Although a radical intermediate was suggested in the reduction of an α,β-unsaturated nitrile [49], diagnostic reaction [50] to differentiate between radical and anion intermediates was carried out to provide allylic alcohol in quantitative yield (Scheme **34**).

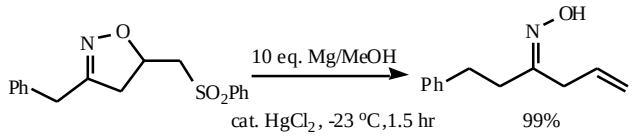
Scheme 36.

Thus the reaction mechanism closely resembles the one suggested for the Zn(Cu) coupled reduction, wherein the carbanion, generated in a stepwise single electron transfer from the metal to the substrate via a carbon-centered radical, opens selectivity to the alkoxide. Similarly, dioxolanyl [17] and carbonate [51] halomethyls provided the corresponding allylic alcohols, as the sole product. Chirality, as expected, was preserved in the corresponding product (Scheme **35**-**36**).

Ring opening of 5-(bromomethyl)- and 5-(phenylsulfonylmethyl)-2-isoxazolines with Mg/MeOH afforded regiospecifically β,γ-enoximes and α,β-enoximes, respectively, depending on the reaction conditions (Scheme **37**-**38**) [52].



Scheme 37.

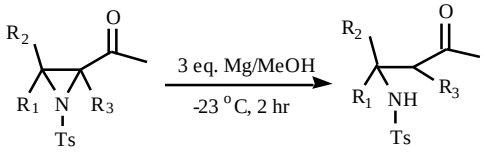


Scheme 38.

In contrast to Zn or Zn/Cu, [53, 18], because the reaction mixture is basic due to $Mg(OMe)_2$, β,γ-enoximes isomerize to afford β,γ- and/or α,β-enoximes.

N-Tosylaziridine ring tethered to an electron withdrawing group such as acyl, ester, and nitrile group underwent C(1)-C(2) bond cleavage products [18].

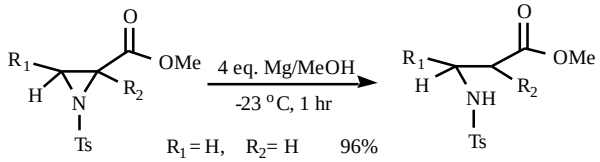
Treatment of 2-acylaziridines with MeOH at –23°C provided the corresponding C(2)-N cleavage products, β-*N*-tosylaminoketones, in excellent yields within 1h (Scheme **39**). A mixture of 1:1 diastereoisomer was obtained in the case of 2-methyl-3-phenylaziridine.



R_1=H,	R_2=H,	R_3=H	97%
R_1=Et,	R_2=H,	R_3=H	93%
R_1=Me,	R_2=Me,	R_3=H	97%
R_1=Ph,	R_2=H,	R_3=Me	98%

Scheme 39.

Compared to the reaction conditions used for 2-acylaziridines, the 2-carbomethoxy aziridines required slightly more Mg (4 equiv). Although a slightly more Mg(4 equiv) is required, 2-carbomethoxyaziridine provided the corresponding *N*-tosyl-β-amino esters in excellent yields (Scheme **40**). This result is in contrast to the use of SmI_2 in THF/EtOH where C(3)-N bond cleavage and C(2)-N bond cleavage gave a mixture of α-and β-amino acids [54]. *N*-Boc aziridine tethered to α,β-unsaturated ester as a mixture of *E* and *Z* isomers was known to be cleaved to give exclusively the *E* isomer of allyl amine as a single product [17]. Diastereomeric substrate (R_1 = Et, R_2 = Me) gave a 1:1 mixture of diastereoisomers.

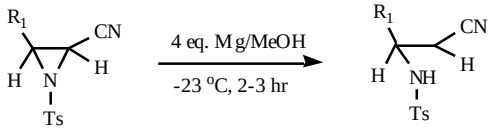


R_1 = H,	R_2= H	96%
R_1 = Me,	R_2= H	94%
R_1 = Et,	R_2= Me	95%
R_1 = Ph,	R_2=H	35%

Scheme 40.

Under standard reaction conditions, 3-phenylaziridine ester provided a mixture of desulfonylated aziridine and the expected cleavage product in 60% and 35% yield respectively. Because desulfonylation of arenesulfonamides by an electron transfer reagent is known [55], direct electron transfer should have caused desulfonylation instead of methanolysis catalyzed by $Mg(OMe)_2$. When modified reaction condition (10 equiv Mg, EtOH/THF, cat. $HgCl_2$, room temp.) was employed [27(c)], desulfonylation was avoided to provide only cleavage product in excellent yield (95%).

The reductive cleavage of cyanoaziridine took place smoothly to afford *N*-tosyl-β–amino nitrile in excellent yield (Scheme **41**). It reveals that the cyano group can play a role as electron acceptor if tethered to a proper functional group which, in turn, can stabilize the resulting radical anion.

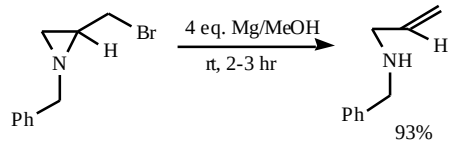


R_1=H	83%
R_1=Ph	80%

Scheme 41.

Reaction of 2-bromomethyl aziridine was slow at –23°C so the temperature was elevated to room temperature. Temperature elevation produced the corresponding allyl amine smoothly even though the C-N bond was not activated (Scheme **42**). The identical cleavage product was obtained in moderate yields (50-53%) by a sonochemical cleavage of the 2-bromomethyl aziridines in the presence of a zinc-copper couple [56].

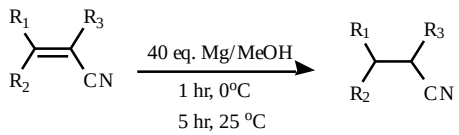
As suggested by Kimpe *et al*. [56], a radical anion generated by single electron transfer from magnesium to bromomethyl aziridines will lose bromide ion to give methyl radical. The methyl radical might undergo either radical cleavage or anionic cleavage by accepting another electron.



Scheme 42.

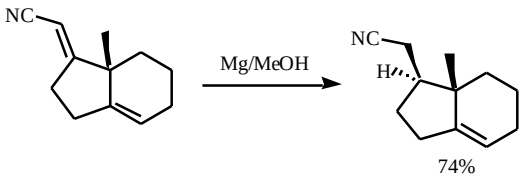
Congugated Double Bond Reduction

Since reduction of conjugated double bond of α,β-unsaturated ketone using Mg / MeOH was first reported in 1929 by Zechmeister and Rom [4(c)], it has been dormant up until it was first employed for the reduction of α,β-unsaturated nitrile to its saturated analog [6(a)]. Soon after reduction of various α,β-unsaturated nitriles with excess amounts of Mg (40 equiv.) in MeOH at room temperature a number of different types of α,β-unsaturated nitriles were reduced in high yields (Scheme **43**) [6(b)].



R_1 : alkyl, cycloalkyl, phenyl, Bn	65~100%
R_2 : H, Me, Bn	
R_3 : H, alkyl	

Scheme 43.



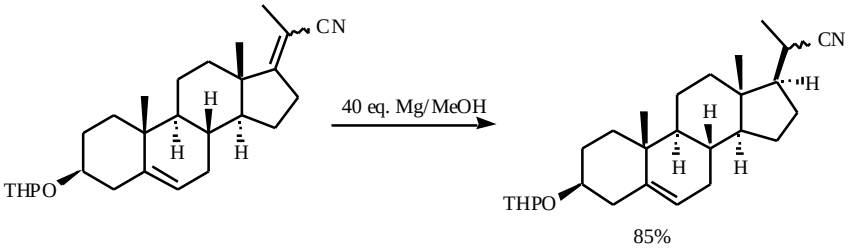
Scheme 44.

And it was compatible with various substitution patterns and with other functional groups. It was pointed out that notable advantages of this method over catalytic hydrogenation was regioselective reduction of a conjugated double bond in the presence of nonconjugated double bond (Scheme **44**). Steroselective reduction of α,β-unsaturated nitriles has been known (Scheme **44**-**45**) [6(i), 57(b), 57(d)].

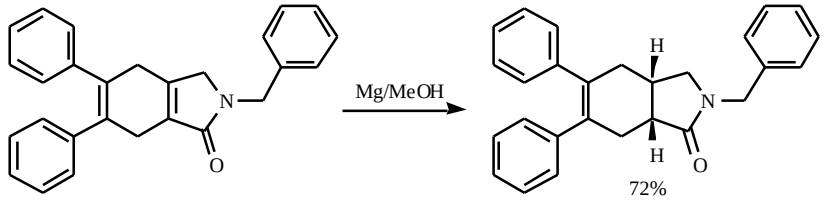
Reduction of the olefinic double bond of α,β-unsaturated esters can be executed with catalytic hydrogenation or with hydride reagents. However, these reduction methods often either lack of selectivity of the isolated double bond and susceptible functionality or suffer from low yields-especially in the case of heteroatom substituted system [60].

In 1986, Ley *et al*. reported that ultrasonic treatment of α-amino-α,β-unsaturated ester with 10equiv Mg in MeOH at room temperature gave the saturated amine in quantitative yield (Scheme **49**) [5(a)].

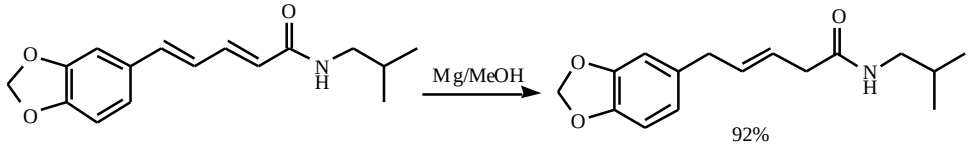
Simultaneously, Pak *et al*. reduced various α,β-unsaturated esters to the corresponding saturated analogue in excellent yields under optimized condition (Table **1**) [5(b)]. While ester exchange took place in the case of sterically unhindered alkyl ester, sterically hindered alkyl group such



Scheme 45.



Scheme 46.



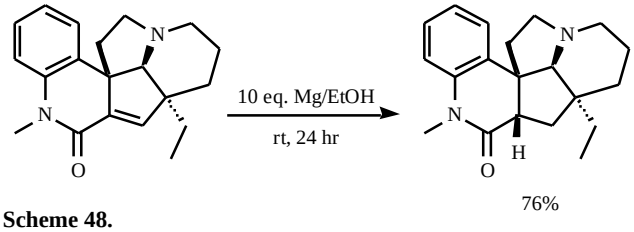
Scheme 47.

Since then, this reaction condition has been widely used in the reduction of α,β−unsaturated nitriles in the presence of other functional groups [57, 6], (g)].

In 1980, Brettle and Shibib selectively reduced an α,β-conjugate double bond of α,β-unsaturated amide in the presence of another olefinic bond (Scheme **46**) [58].

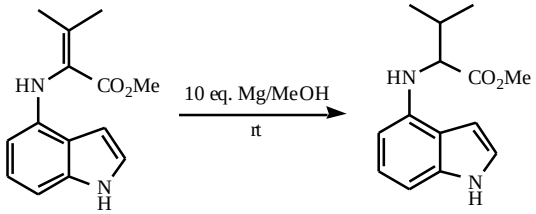
In the case of the amide group which was doubly conjugated, the α,β-double bond was shifted to β,γ-position in *trans* isomer (Scheme **47**) [59].

Reduction followed by epimerization led to the formation of more stable isomer upon prolonged reaction time when EtOH instead of MeOH was used (Scheme **48**) [7(c)].



Scheme 48.

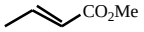
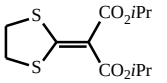
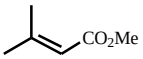
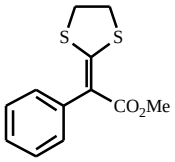
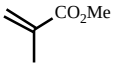
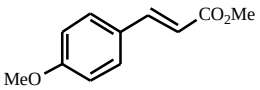
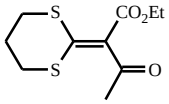
as isopropyl, t-butyl group was intact for exchange into its methyl ester. It was also applicable to the ketene dithioacetal derivatives where the conjugation was extended with dithiolane group to give the corresponding half protected 1,3-dicarbonyl compounds in high yields [61]. This type of compound might have been encountered with difficulty because of its susceptible nature of the sulfur atom to catalytic hydrogenation or hydride reagent [62].



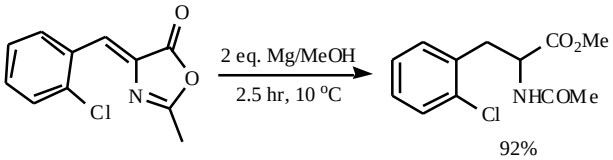
Scheme 49.

Selective reduction of olefinic double bond of azalactone was followed by a ring opening product (Scheme **50**). Similar transformation was performed under different

Table 1. Reduction of α,β-unsaturated esters with Mg/MeOH [61].

Substrate	Yield	Substrate	Yield	
	98%		93%	
	100%		90%	
	94%			
	96%		87%	Ref [70]

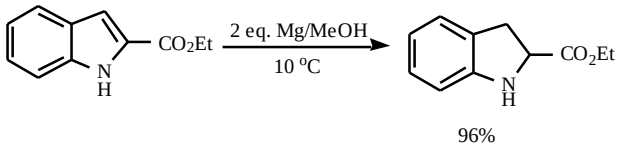
Reaction condition: 2eq. Mg/MeOH, 2.5hr, 10°C



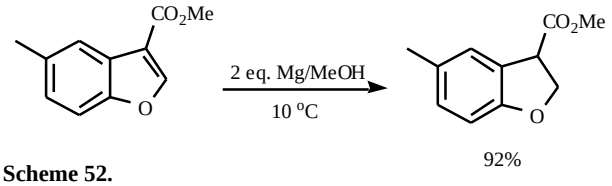
Scheme 50.

reaction conditions such as catalytic hydrogenation under high pressure [63] or catalytic transfer hydrogenation using palladium(II)chloride [64].

The most striking feature of this reagent is the reduction of aromatic double bond, which is conjugated with the ester group. Thus indole-2-carboxylates were reduced smoothly into the corresponding indolines almost quantitatively (Scheme **51**). Even though a number of methods to reduce substituted indoles to its indolines are known, reduction of the electron withdrawing group substituted indoles such as indole-2-carboxylate is not straightforward and no other method is comparable to Mg/MeOH in its simplicity and yields [65].



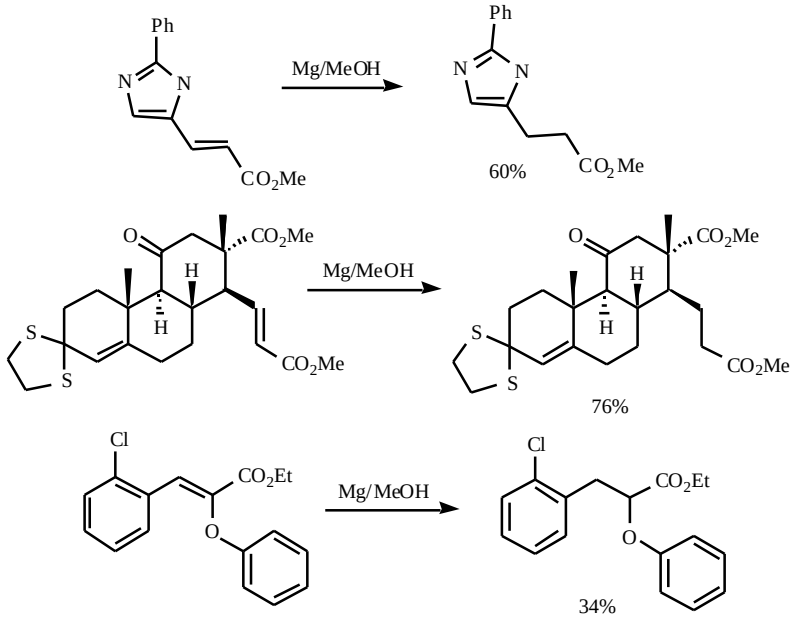
Scheme 51.



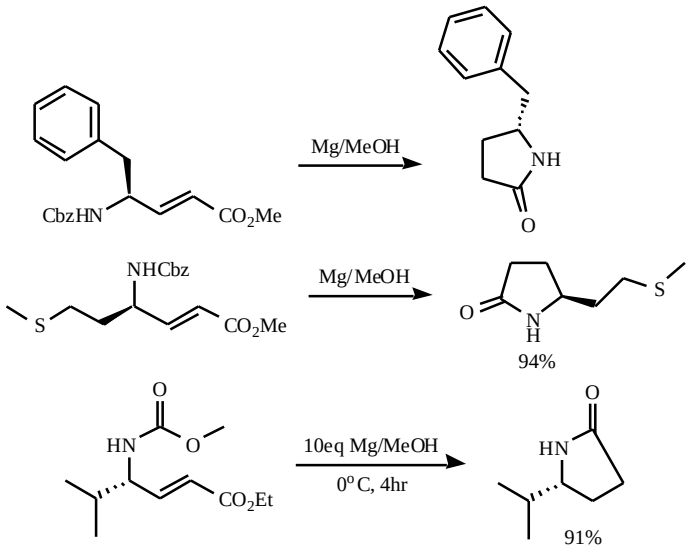
Scheme 52.

Similarly benzofuran carboxylate was reduced (Scheme **52**) [5(c)].

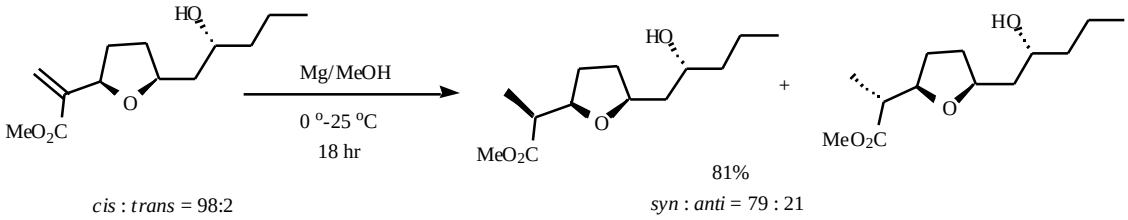
Since the ability to reduce olefinic double of α, β - unsaturated esters had been proved in 1986, numerous examples of reduction in the presence of other functionalities have been appeared in the literature (Scheme **53**) [66].



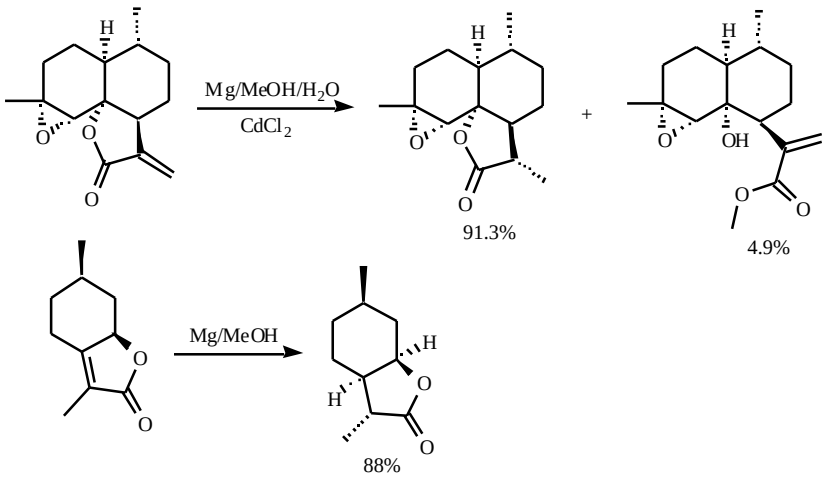
Scheme 53.



Scheme 54.



Scheme 55.



Scheme 56.

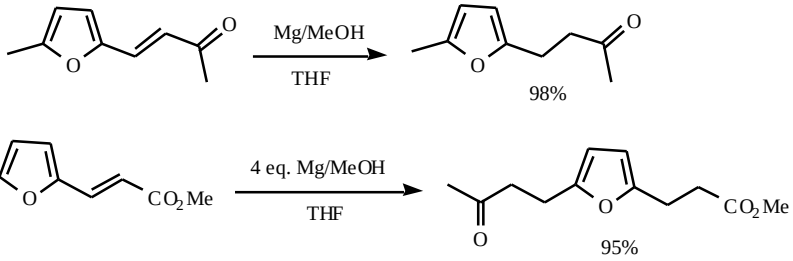
Reduction of *N*-Cbz-γ-amino-α,β-unsaturated esters was followed by concomitant deprotection of *N*-Cbz group and cyclization to provide pyrrolidones (Scheme **54**). Various 5-substituted 2-pyrrolidones were prepared from *N*-protected γ-amino-α,β-unsaturated carboxylates. Reduction of the conjugated double bond followed by cyclization *via* deprotection of carbamate catalyzed by $Mg(OMe)_2$ would lead to 2-pyrrolidone formation [67].

Chelation controlled stereoselective reduction of polyoxygenated systems was tested in moderate stereo-selectivity (Scheme **55**) [68], whereas catalytic hydrogenation yielded 50:50 mixtures of *syn* and *anti* products [69]. It was postulated that stereoselectivity is due to the formal delivery of hydrogen to the less hindered face of a cyclic complex between the substrate and Mg(II).

In a highly strained lactone, lactone ring survived during double bond reduction (Scheme **56**) [69].

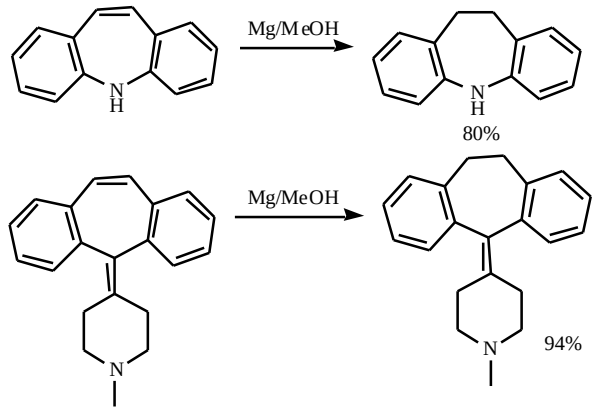
Chemoselective reduction of double bonds conjugated with carbonyl groups and furan rings has been accomplished by using Mg/MeOH reducing system (Scheme **57**).

The chemoselective reduction of double bonds conjugated with a furan nucleus is a rather troublesome case, as a consequence of the easy saturation of the heterocyclic moiety [70], and the wellknown sensitivity of furans to acids or bases [71]. Although heterogenous hydrogenation over palladium catalysts has proven to be an efficient method of carrying out this reduction [72], Mg/MeOH is an alternate methodology that can supersede the well-known limitations of catalytic hydrogenation [73].



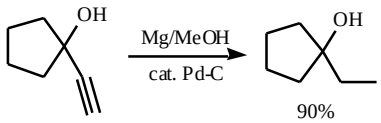
Scheme 57.

Although an isolated carbon-carbon double bond was inert for Mg/MeOH, olefinic double bond conjugated with C-C double bonds was reduced efficiently (Scheme **58**) [74].



Scheme 58.

Even though the non-activated triple bond of propargyl alcohol also reduced into the saturated analog in the presence of a catalytic amount of Pd-C(10%), it is apparent that Mg/MeOH is a source of hydrogen for catalytic hydrogenation since the isolated triple bond was inert to Mg/MeOH (Scheme **59**) [75].



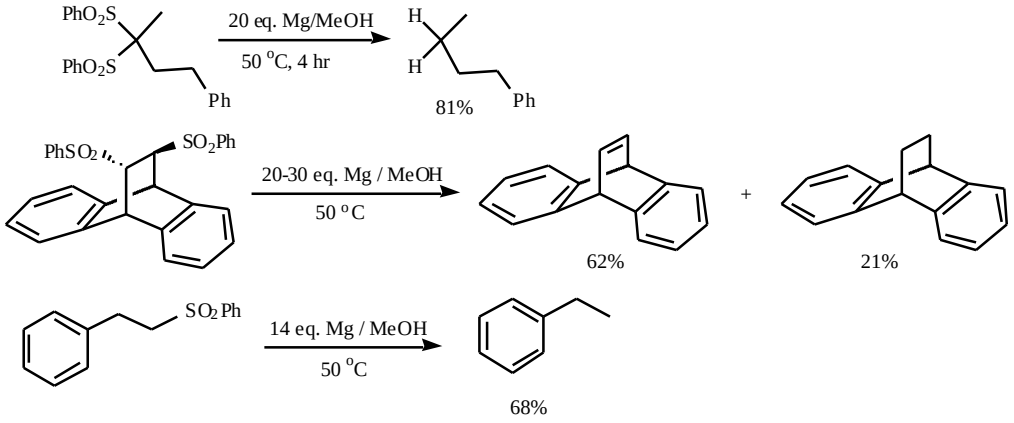
Scheme 59.

Desulfonylation

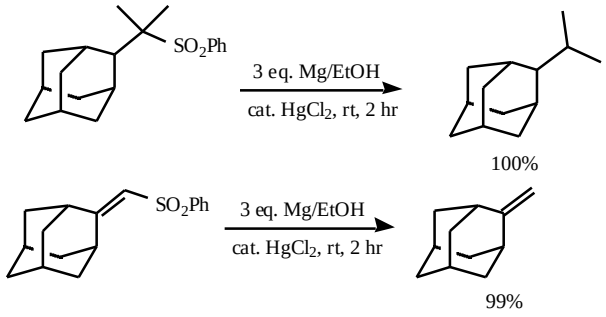
Desulfonylation can be achieved regardless of the kind of atom to which the sulfonyl group attached. Therefore reductive cleavage of C-S, N-S, and O-S bonds of C-SO_2Ar, N-SO_2Ar, and O-SO_2Ar, respectively, can be performed with Mg /MeOH. Although a number of reagents are available for cleaving the benzenesulfonyl group sodium amalgam either in alcohol or buffered with anhydrous disodium hydrogen phospate is the most frequently employed one among other electron transfer agents such as lithium in aliphatic amine, sodium in alcohol, aluminum amalgam in aqueous THF and Grignard reagents with nickel or palladium catalysts [76]. In order to carry out desulfonylation in a controlled manner and avoid handling cumbersome active alkali metals it is desirable to develop a milder and more efficient desulfonylating agent. Previously Mg/MeOH was utilized for the desulfonylation of primary and secondary alkyl phenyl sulfones [77(a),(c)] and 1,1-bis(benzene sulfones) [77(b),(c), (d)], however, it was necessary to use an excess amount of highly activated magnesium (20-30 equiv) in methanol at 50°C to complete the reaction (Scheme **60**). Geminal sulfones underwent reductive cleavage to give their saturated analog, and 1,2-bis(sulfone) gave a mixture of olefin stemmed from reductive elimination along with their saturated analog [77(c), 77(d), 78(d)].

Under optimized conditions it was Mg/EtOH rather than Mg/MeOH in the presence of catalytic amount of $HgCl_2$ that facilitated the cleavage reaction. Reductive cleavage of alkyl and vinyl phenyl sulfones were carried out with 3 equiv of Mg in absolute EtOH in the presence of catalytic amount of $HgCl_2$ at room temperature (Scheme **61**) [8(e)].

Moderate product yields were obtained by either employing Mg /MeOH suffering from the loss of excess amounts of Mg [78] or in the presence of a catalytic amount of $HgCl_2$ [79(a)-(c)] with THF as a cosolvent [79(d)-(e)] to control the reaction rate. Regardless of sp^3 or sp^2 character of the carbon atom to which the sulfur atom is attached [78(d)], desulfonylation proceeded smoothly. But in some cases product from the electron shift during C-S bond cleavage



Scheme 60.

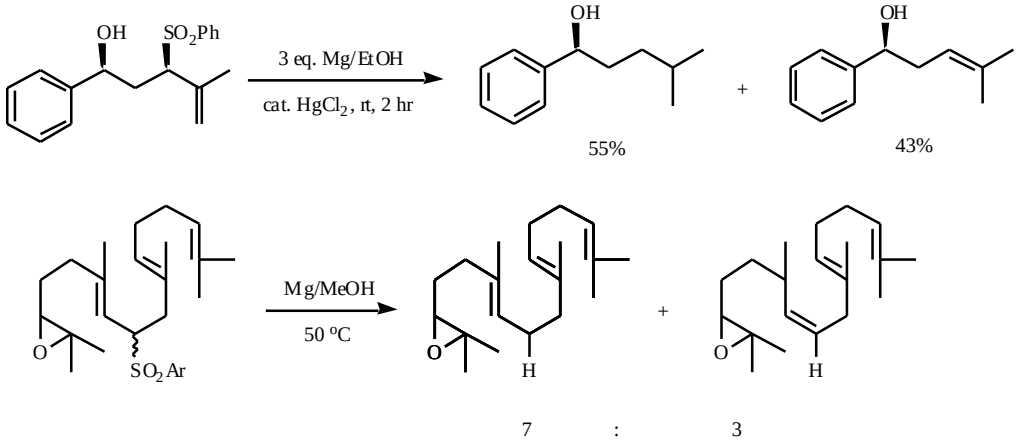


Scheme 61.

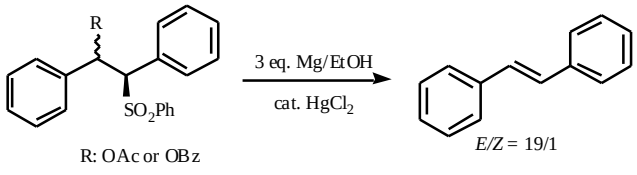
was observed. So allyl sulfone gave a mixture of the two isomeric olefins, one of which is a double bond shifted product (Scheme **62**) [78(a)].

alkyl sulfone anions to carbonyl compounds and subsequent reductive elimination, the second step has been carried out most frequently by sodium amalgam or sometimes by lithium amalgam which is cumbersome in handling. More recently SmI_2 has been used for reductive elimination of the sulfonyl group [81]. Relatively poorer yields and isomeric ratio were obtained. Reductive elimination of β-hydroxy sulfone derivatives during Julia olefination was conveniently performed with 3 equiv of Mg powder without activation in absolute EtOH in the presence of a catalytic amount of $HgCl_2$ at room temperature (Scheme **63**) [27(a)].

Threo- and *erythro*- β-acetoxy (or benzoyloxy) phenylsulfones gave *E*-alkenes exclusively regardless of the stereoisomeric configuration of the starting sulfones, and *E*-stilbene was obtained as a major product (*E/Z* = 19/1) (Scheme **63**). The over reduction of stilbene to obtain 1,2-



Scheme 62.

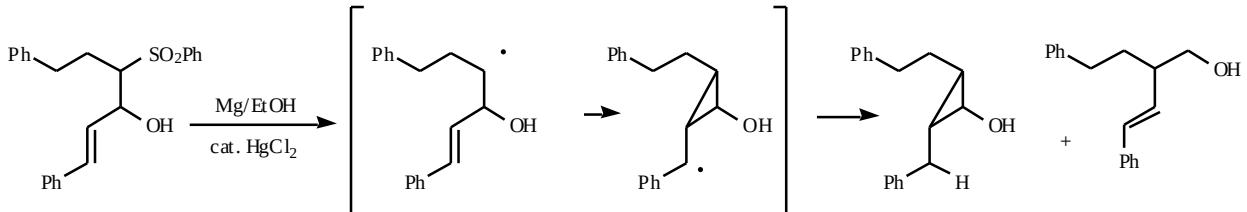


Scheme 63.

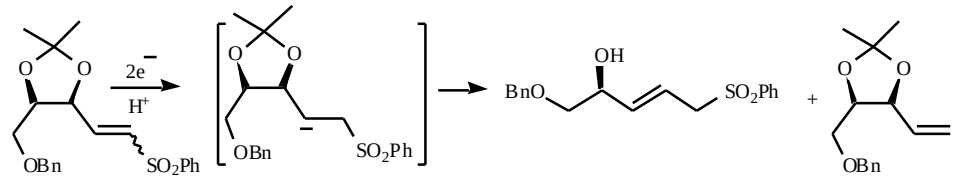
Previous observation of reductive elimination during desulfonylation of 1,2-bis(sulfones) [77] along with this double shift product envisaged Julia olefination [80]. In the course of Julia olefination, which operates by the addition of

diphenylethane did not occur with Mg/MeOH [9]. In order to prove the presence of a radical intermediate during the desulfonylation, 1,6-diphenyl-3-hydroxy-4-phenylsulfonyl-1-hexene was subjected to the same condition as above. A major product of 2-phenylmethyl-3-(2-phenylethyl)cyclopropanol resulting from intramolecular trapping of a radical intermediate and a minor product of the rearranged homoallylic alcohol were obtained (Scheme **64**) [11].

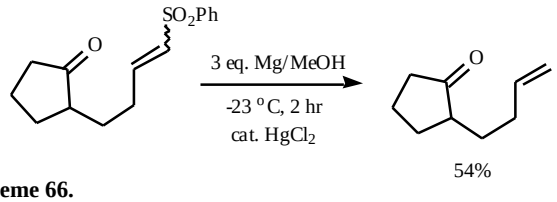
In the case of α,β-unsaturated sulfone, a mixture of β-cleavage and desulfonylation products was obtained by treating dioxolane tethered to α,β-unsaturated phenylsulfone with Mg in MeOH (Scheme **65**) [11].



Scheme 64.

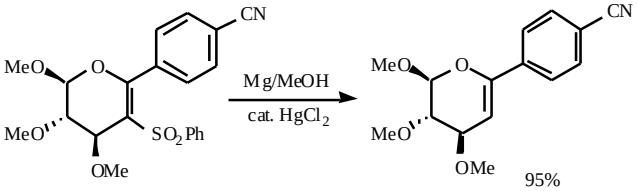


Scheme 65.

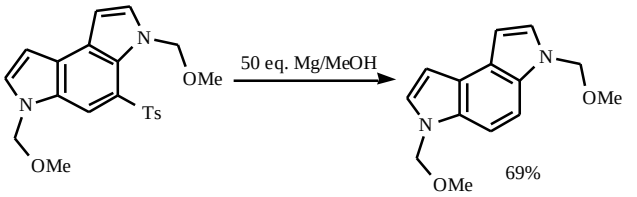


Scheme 66.

On the other hand, α,β-unsaturated sulfone without leaving group at β-position or aryl sulfone furnished only desulfonylated product (Scheme **66**-**68**) [11, 78(d), 79(c)]. Large excess amounts of Mg were required for arylsulfone compared to vinyl sulfone. It is interesting to note that tosyl group instead of tolyl group was eliminated out of the two C-S bonds (Scheme **68**) [79(c)].

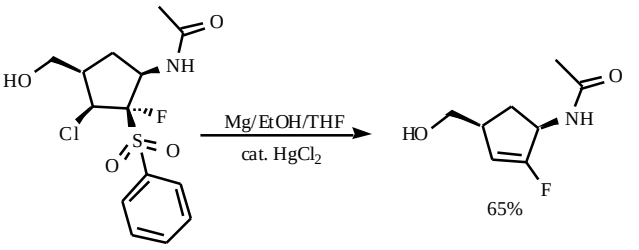


Scheme 67.

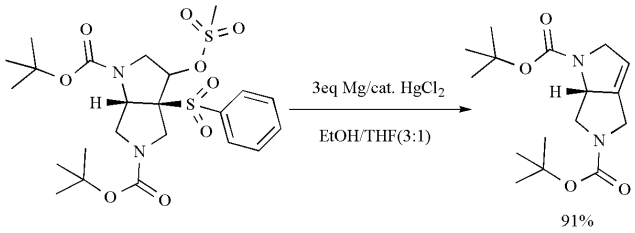


Scheme 68.

It seems that desulfonylation of α,β-unsaturated sulfone proceeds through the heterolytic β–cleavage of the β–sulfonyl carbanion. In case, there is an extra leaving group (Scheme **65**) competition between the sulfonyl group and the leaving group at α-position of carbanion is taking place. Whereas, only the sulfonyl group exists in the carbanion, simple elimination of sulfonyl group occurs to give alkene product (Scheme **66**). Desulfonylation of alkyl or aryl phenyl sulfones with Mg/EtOH implied homolytic cleavage of a C-S bond [8(e)]. Desulfonylation of alkyl or aryl phenyl sulfones proceed *via* the homolytic cleavage of the anion radical. And desulfonylation α,β-unsaturated phenyl sulfones proceeds *via* heterolytic β-cleavage of the β-sulfonyl carbanion. Kende *et al.* reported a similar result using imidazoyl sulfone instead of phenylsulfone as the substrate under reductive elimination condition (SmI_2/THF) and suggested the presence of a radical intermediate [81(d)]. Other leaving groups such as chloride [82] or sulfonate [83] at β-position underwent β-elimination during desulfonylation (Scheme **69**-**70**).



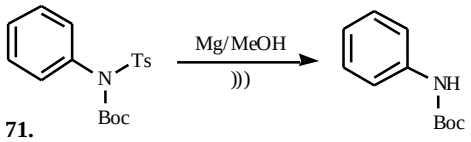
Scheme 69.



Scheme 70.

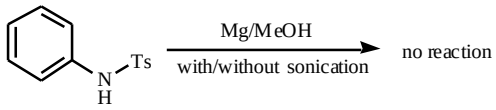
Among a number of protection methods for amine, sulfonylation with various substituted phenylsulfonyl chlorides has been widely used since the resulting sulfonamide is usually a crystalline solid and resistant to nucleophilic attack [84]. For the deprotection of a typical *N*-tosyl group, harsh conditions such as sodium in liquid ammonia [85], sodium amalgam in a protic solvent [86], sodium naphthalenide [87], or refluxing 48% HBr in the presence of phenol [88] were conventional methods of choice.

Milder deprotection methods including SmI_2 [89], *n*-Bu_3SnH-AIBN [90] and electrolysis [91] were reported recently and complemented previous severe conditions. Desulfonylation of doubly activated amines such as *N*-Boc or ***N***-acylarenesulfonamide using Mg/MeOH under ultrasonic conditions was reported (Scheme **71**) [92]. Under these conditions parent amines are limited to only primary amines which should be activated by *N*-Boc or *N*-acyl group for desulfonylation. Additional effort was also made by modifying arenesulfonamide to the more labile heteroarenesulfonamides [93,94].



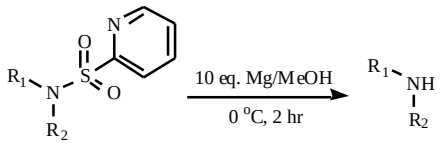
Scheme 71.

While activated *N*-Boc-*N*-tosylaniline was easily desulfonylated to *N*-Boc aniline, desulfonylation without activation was inert even with sonication(Scheme **72**).



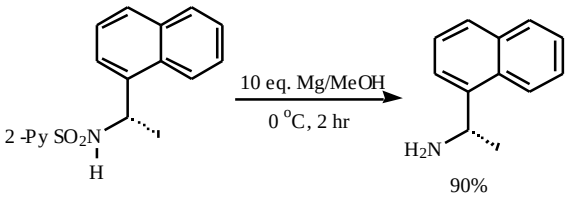
Scheme 72.

Instead of *p*-toluenesulfonyl or phenylsulfonyl group, which were appropriate for desulfonylation with activiation, desulfonylation of pyridine-2-sulfonamides derived from various primary and secondary amines was achieved using Mg / MeOH without activation (Scheme **73**) [95].



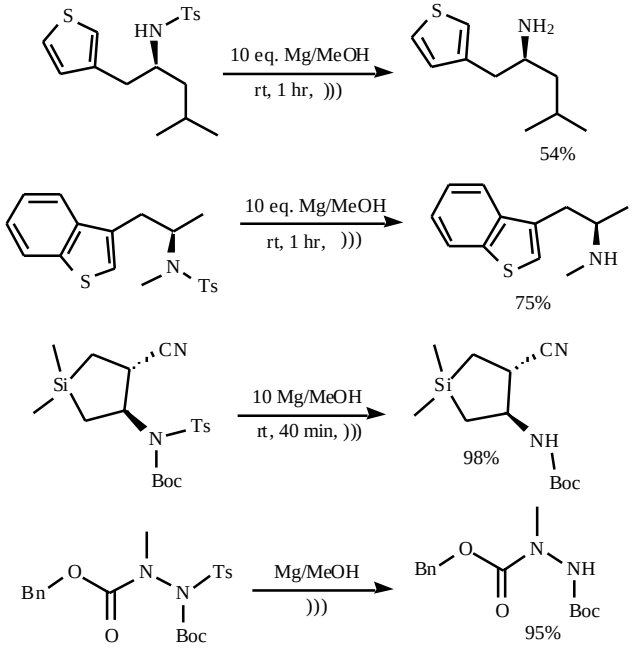
R_1= Ph R_2= H	86%
R_1= Ph R_2= Ph	96%
R_1= Bn R_2= H	77%
R_1= Bn R_2= Ph	93%
R_1= Bn R_2= Me	86%

Scheme 73.



Scheme 74.

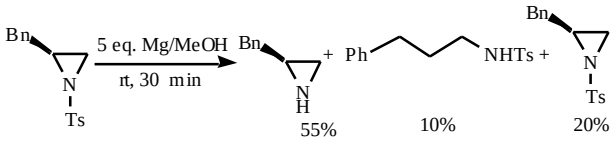
In contrast to resistant *p*-toluenesulfonamide desulfonylation proceeded readily to provide the parent amines in good yields. In general, the reaction rate for desulfonylation was much faster than that of SmI_2 with either *p*-toulenesulfonamides(1.5~11hr) [89] or 2-pyridinesulfonamides (4hr) [95]. Chiral amine sulfonamides were subjected to the reaction condition. No racemization was observed (Scheme **74**).



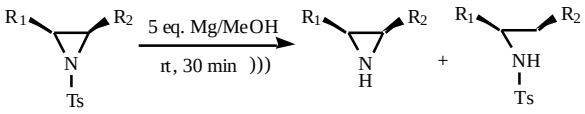
Scheme 75.

Regardless of primary or secondary amine the corresponding stable solid pyridine-2-sulfonamides were conveniently desulfonylated with Mg /MeOH. It is apparent that the 2-pyridinesulfonyl group can be used as a convenient amine protecting group when Mg/MeOH is employed as a desulfonylating reagent. Recently desulfonylation of inactivated sulfonamides of primary amine and secondary aliphatic amine under ultrasonic conditions appeared in the literature (Scheme **75**) [96]. Although yields were much lower compared to its *N*-activated substrate, deprotection of the tosyl group took place, while deprotection of the aromatic amine was reluctant to cleave the S-N bond.

Desulfonylation of *N*-tosylaziridines was reported with 5 equiv of Mg/MeOH at room temperature [97]. The reaction resulted in a fast consumption of the metal and production of aziridine, along with up to 20% of starting aziridine as well as 10% of ring opening product (Scheme **76**). However, when the reaction was allowed to proceed under ultrasonic conditions, good yields of the corresponding desulfonylated aziridines were obtained (Scheme **77**) [92(b)]. The 2-phenyl substituted aziridine gave a good yield of the NH aziridine. These mild reaction conditions are also compatible with other functional groups. For instance, reduction of carboxylate aziridine provided a 75% yield of the desulfonylated aziridine accompanied by only 12% of the ring opening product [98]. A similar regioselective ring opening process has been observed in the reduction with SmI_2 of aziridine-2-carboxylates [98].



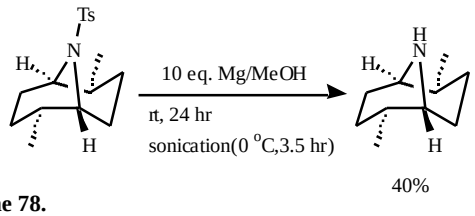
Scheme 76.



R_1= Ph, R_2 = H	65%	8%
R_1= Bn, R_2= H	78%	-
R_1= Bn, R_2= CO_2Cy	75%	12%

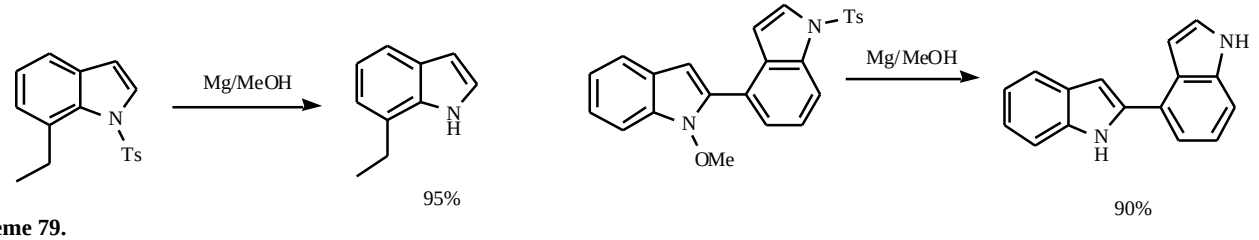
Scheme 77.

An attempt to deprotect *N*-Ts group of azabicyclic substrate under sodium and liquid ammonia, failed to give desired amine. However, reductive cleavage of the *N*-Ts group using Mg/MeOH furnished the desired product in moderate yield (Scheme **78**) [99].



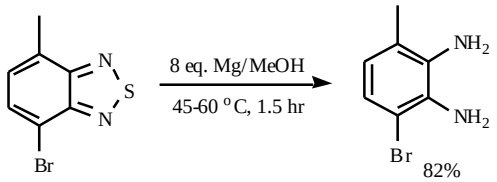
Scheme 78.

Desufonylation of *N*-*p*-tosylindole [100] and *N*-*p*-tosylpyrrole [101] has been encountered frequently in the literature (Scheme **79**).



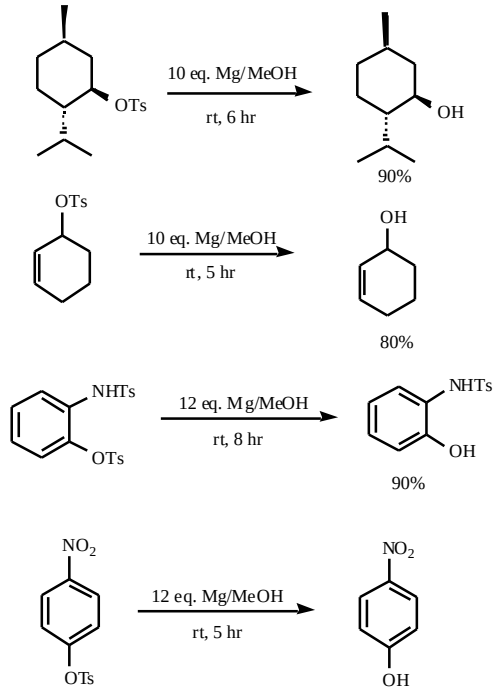
Scheme 79.

For the reduction of 2,1,3-benzothiadiazoles to 1,2-benzenediamines, Mg/MeOH was employed conveniently to cleave S-N bonds (Scheme **80**) [101]. In the case of bromo substituted 2,1,3-benzothiadiazoles, the corresponding 1,2-benzenediamine was obtained exclusively in 82% yield. Less than 2% of debrominated product was obtained.



Scheme 80.

Alkyl and aryl sulfonates also can be cleaved with Mg/MeOH regenerating the corresponding alcohols (Scheme **81**) [101].

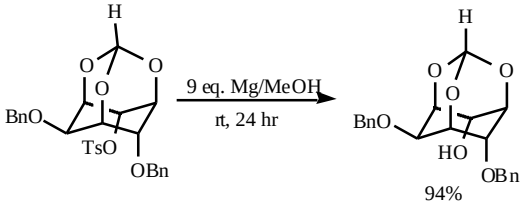


Scheme 81.

All sulfonates are labile and undergo elimination and substitution reactions very easily. Convenient methods for this transformation are scarce in the literature. The earlier methods for conversion of *p*-toluenesulfonates in alcohols include: i) reduction with sodium amalgam in ethanol [102], ii) hydrogenolysis with nickel [103], iii) reduction with sodium in liquid ammonia [104] and iv) sodium naphtalene in tetrahydrofuran. [105].

When compared to these processes, Mg/MeOH is a simple, mild and efficient approach for conversion of *p*-toluenesulfonates in alcohols. Further, arylsulfonates, which are highly stable when compared to alkyl tolenesulfonates, are widely in use as protective agents for the hydroxyl group of phenols [106]. The resulting alcohols did not undergo epimerization under the reaction condition. The mechanism was suggested as one similar to that suggested by Kovacks and Ghatak for the cleavage of *p*-toluenesulfonamides with sodium in liquid ammonia [107].

Sulfonylated derivatives of *myo*-inositol orthoesters were cleaved using Mg/MeOH to regenerate the correspondning *myo*-inositol orthoester derivatives. These methods of protection-deprotection have been used for the efficient synthesis of enantiomers of 2,4-di-*O*-benzyl-*myo*-inositol and 2-*O*-benzyl-*myo*-inositol (Scheme **82**) [108].

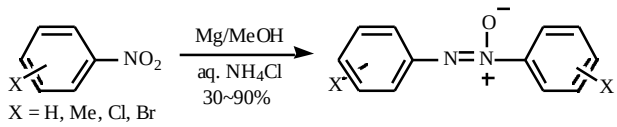


Scheme 82.

Reduction of Functional Groups

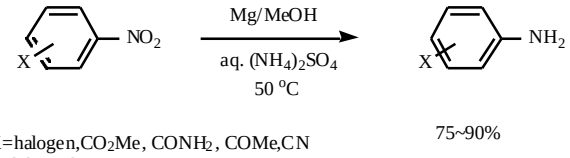
Reduction of aromatic nitro compounds often proceeds to generate mixtures of nitroso and hydroxylamine products which then condense to form azoxy and eventually azo compounds. Among the various reducing agents used to reduce nitroarenes to azo compounds is a frequently used mixture of Zn and NaOH [109]. Sometimes Zn/AcOH/Ac_2O [110], Sn(II) in a basic media [111], Na-Pb alloy [112], or Tl/EtOH [113] were used for the reduction of aromatic nitro compounds to azoxy derivatives.

Zechmeister and Rom reported for the first time that aromatic nitro compounds are reduced to azoxy compounds in moderate yields (30~90%) with Mg metal in a mixed solvent of methanol and a small amount of saturated aqueous NH_4Cl solution (Scheme **83**) [4(a),(c)]. If the large excess amount of Mg was used, azoxy compounds resulting from nitro compounds would further reduce to hydrazines. They also obtained azo or hydroxylamine derivatives depending upon reaction conditions, (mainly the amount of Mg used). Azoxy compounds were reduced under control to the corresponding azo products with Mg in boiling ethanol in quantitative yields [114].

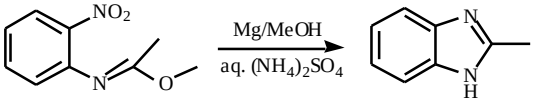


Scheme 83.

Further reduction to amine could be achieved by employing a slightly different reaction condition using ammonium sulfate as a promoter (Scheme **84**-**85**) [115].

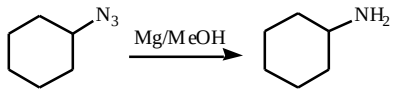


Scheme 84.



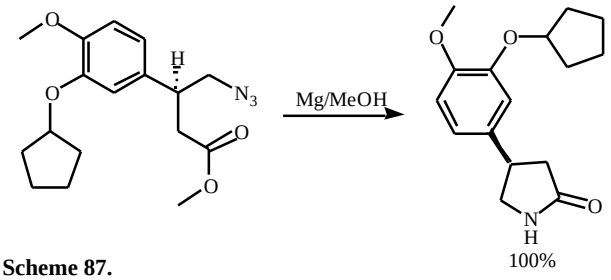
Scheme 85.

In 1988, Maiti *et al.* reported that aryl and aliphatic azides were reduced to the corresponding primary amines with excess Mg/MeOH in excellent yields (94~99%) (Scheme **86**) [116].



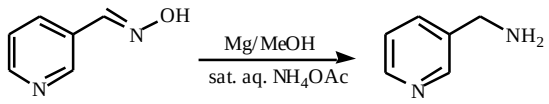
Scheme 86.

Reductive cyclization of the γ-azido methyl butanoate backbone was performed to provide 2-pyrrolidone in excellent yield (Scheme **87**) [117].



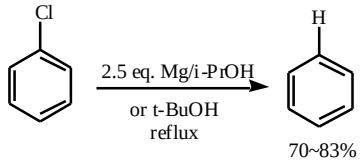
Scheme 87.

In 1930, Zechmeister and Truka reported that Mg reduces various aromatic aldimines to corresponding saturated primary or secondary amines [4(b),118]. Oxime was also reduced into amine in the presence of saturated aqueous NH_4OAc (Scheme **88**) [119].



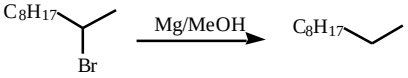
Scheme 88.

In 1929, Zechmeister and Rom [4(c)] also found the reduction of aryl halides with Mg in absolute methanol at room temperature. Since then, Bryce-Smith *et al*. reported that organic halides, although fluorides react less readily, are reduced with excess Mg in boiling alcohols such as isopropanol or *tert*-butanol (Scheme **89**) [9], [120]. Under this reaction condition, secondary and tertiary halides underwent elimination to give olefin as the major product [120(b)].



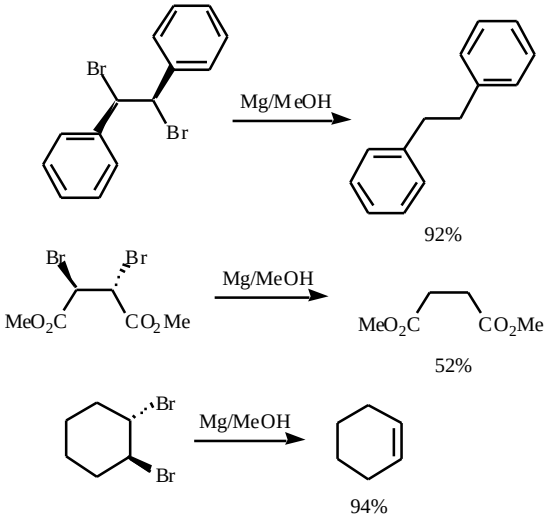
Scheme 89.

Recently, Hutchins and Suchismita reduced alkyl, aryl, and alkenyl halides to the corresponding dehalogenated products with excess Mg/MeOH at room temperature, whereas aryl chlorides and vinyl bromide were not reduced (Scheme **90**) [9].



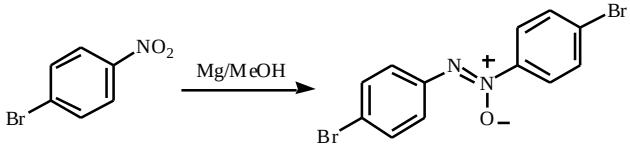
Scheme 90.

Vicinal dibromo compound resulted in olefin which was further reduced to its saturated analog if it was conjugated with an electron withdrawing group (Scheme **91**) [118].



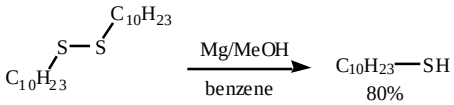
Scheme 91.

However, in the presence of nitro group, dehalogenation was harnessed (Scheme **92**) [121].



Scheme 92.

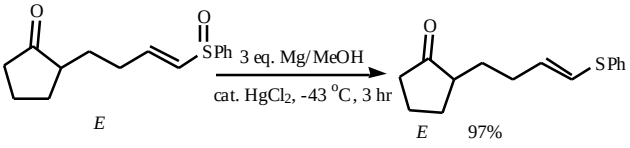
Reduction of disulfide to thiol was also performed conveniently with Mg in methanol (Scheme **93**) [122].



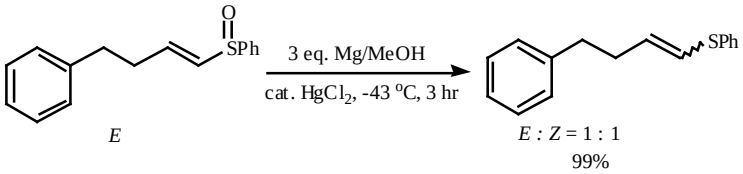
Scheme 93.

Deoxygenation

Deoxygenation of sulfoxide [8(c)], *N*-oxide [123], phosphine oxide [124] proceeded smoothly with Mg /MeOH. It is noteworthy that various reagents are known for deoxygenation of sulfoxides [125]. *E* and *Z* isomers of l-alkenyl phenyl sulfoxides were subjected to the standard conditions to give the corresponding sulfides in quantitative yields (Scheme **94**-**95**). Deoxygenation reaction proceeded with or without isomerization of the double bond depending on the nature of the substrates. Complete isomerization occurred to give the identical product mixture of 1:1 *E* and Z sulfides from each of the substrates (Scheme **95**). On the other hand geometry of double bond was retained completely in keto sulfoxide (Scheme **94**).

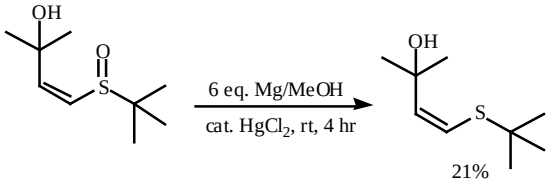


Scheme 94.



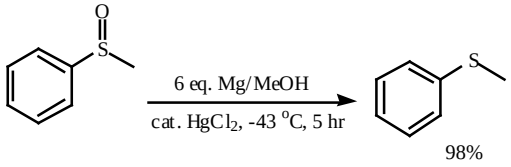
Scheme 95.

Under the same reaction condition, 1-alkenyl alkyl sulfoxides (Scheme **96**) were inert. Even in the elevated reaction temperature only a small amount of the corresponding sulfides was obtained with mostly the unreacted starting materials. Sterically compressed *cis*-configuration of the substrates was retained in the product to provide *cis*-sulfides.



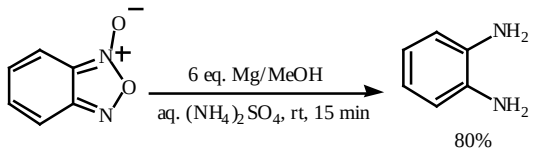
Scheme 96.

In contrast, the reduction of alkyl phenyl sulfoxides (Scheme **97**) was so slow at low temperatures that excess amounts of Mg (6 equiv.) and prolonged reaction time (5 h) were required to complete the reaction. However, the yields of the corresponding sulfides are nearly quantitative.



Scheme 97.

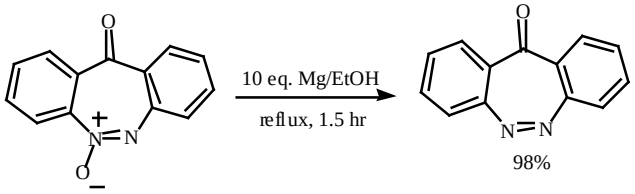
While 2,1,3-Benzooxadiazole-1-oxides were known to be deoxygenated to form the corresponding furazan by trialkyl phosphites [126], Mg/MeOH could reduce to the corresponding diamine (Scheme **98**) as a sole product [115(a)].



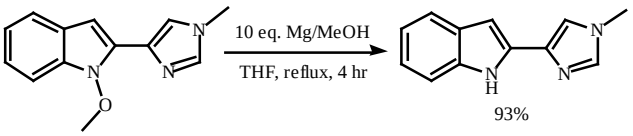
Scheme 98.

Azoxy compounds were reduced under control to the corresponding azo products with Mg in boiling ethanol in quantitative yields (Scheme **99**) [123(a)].

Deprotection of *N*-alkoxy group was done by Mg/MeOH (Scheme **100**) [123(b),(c)].

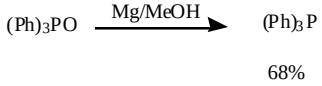


Scheme 99.



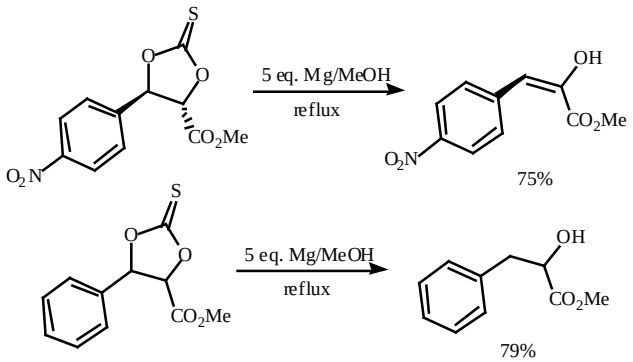
Scheme 100.

Deoxygenation of phosphin oxide was known (Scheme **101**) [124].



Scheme 101.

The cyclic thionocarbonates of aromatic 2,3-dihydroxy esters, which have an electron-withdrawing group, undergo deoxygenation to form α-ketoesters or α-hydroxy esters, depending on the type of electron-withdrawing group (Scheme **102**) [127]. Destabilization of a generated benzylic radical causes hydrogen abstraction to furnish α-ketoester. On the other hand, without the destablizing effect, the benzylic radical undergoes proton abstraction to give an α-hydroxy ester.



Scheme 102.

In conclusion Mg/MeOH is a reagent of choice for electron transfer reagent for versatile organic reactions. It is a simple to use, inexpensive, and an environmentally benign reagent compared to other methods such as SmI_2 or n-Bu_3SnH.

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