

## Chelation Assistance in the Activation of C-S and C-O Bonds

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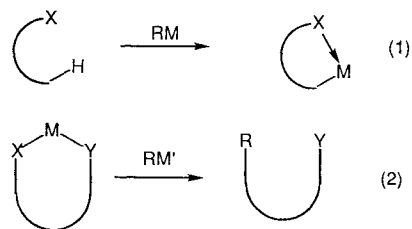
**Abstract:** A chelation approach to activate C-S and C-O bonds is described. In the area of organosulfur chemistry, the theme is based on the formation of a chelation complex which results in the enhancement of the reactivity of the aliphatic carbon-sulfur bonds in the nickel-catalyzed cross coupling reactions with the Grignard reagent. Various neighboring heteroatom substituents (OR, OH, NR<sub>2</sub>, SR as well as another dithioacetal group) can facilitate the olefination of a dithioacetal group. Depending on the relative position of the newly formed double bond and the remaining dithioacetal moiety, tandem olefinations of bisdithioacetals occur to yield the corresponding dienes under these conditions. Polythioethers afford the corresponding dienes via  $\beta$ -sulfur elimination process. 1,3-Dimercapto- and 1,3-dithiolatopropanes undergo desulfurative cyclopropanation under these reaction conditions. The reactions of dihydrothiopyrans with MeMgI in the presence of the nickel catalyst proceeds smoothly to give vinyl cyclopropanes. Ketals containing a neighboring heteroatoms react with the Grignard reagent in aromatic solvents regio- and stereoselectively. The reactions of acetonide derivatives of monosaccharides under these conditions afford the corresponding products which have only one or two free hydroxy groups depending on kind of the Grignard reagents employed. Tunable chiral diols are obtained from the reactions of 2S,3S-threitol bisketals with Grignard reagents or with LiAlH<sub>4</sub>/AlCl<sub>3</sub>.

The reactions of benzylic acetals, prepared from these chiral diols and aromatic aldehydes, with aryl or secondary or sterically hindered Grignard reagents give the corresponding retentive ring-opening products in high diastereoselectivity.

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### 1. Introduction

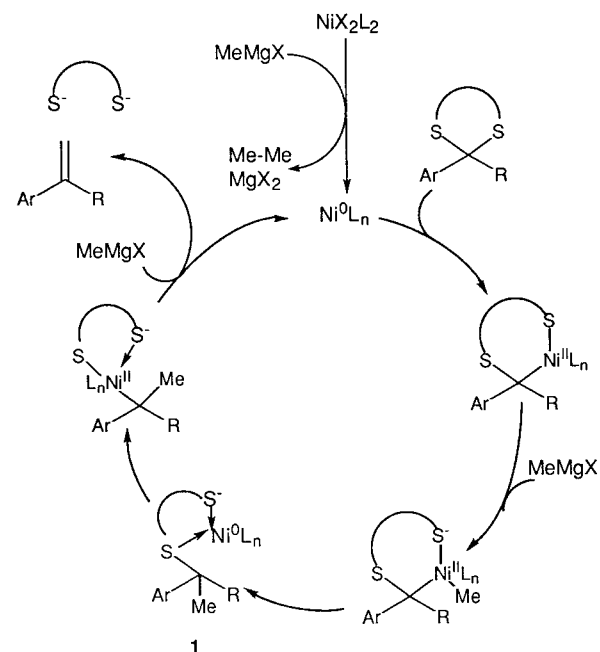
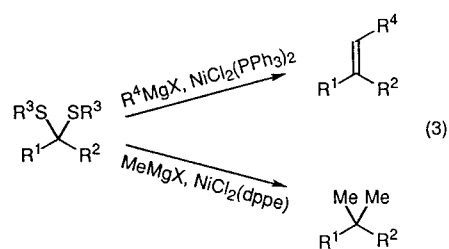
Chelation demonstrates a unique role in the ever burgeoning field of fascinating organic transformations. By means of chelation, metallation of an otherwise unreactive C-H bond has paved the way for the regio- and/or stereoselective functionalization of substrates of different structural variety (eq 1).<sup>1</sup> Due to the chelate formation the organometallic product obtained is stabilized. The carbon-heteroatom bonds in certain coordinated complexes are known to be reactive;<sup>2</sup> and substrates containing more than two heteroatoms in proximity can readily form chelate complexes.<sup>3</sup> Like the chelate-assisted reaction of the C-H bond mentioned above, these heteroatom moieties can interact *symbiotically* with the metallic species such that one of these carbon-heteroatom bonds can be activated (eq 2). In other words, the reaction will occur if and only if these heteroatoms are coordinating to the metal *simultaneously*; the chemistry of these carbon-heteroatom bonds will behave differently when they are alone. Depending on the sort of the heteroatom, the properties of the metallic species, the nature of the substrate, and the reaction conditions, selective transformation of a carbon-heteroatom bond to a carbon-carbon bond can be achieved. This Account will focus on the personal experience on the discovery of the selective activation of the aliphatic carbon-sulfur and carbon-oxygen bonds leading to the carbon-carbon bond formation.



### 2. Activation of Aliphatic Carbon-Sulfur Bonds

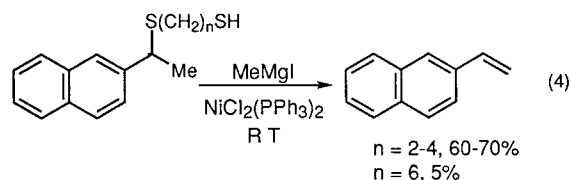
#### 2.1. Background

The nickel catalyzed cross coupling reactions of allylic, benzylic and vinylic organosulfur compounds with Grignard reagents have been extensively investigated.<sup>4,5</sup> The extension of this reaction to the dithioacetal functionality has demonstrated a useful methodology for the olefination as well as geminal dimethylation of a carbonyl equivalent (eq 3).<sup>6-8</sup> In this regard, the dithioacetal moiety can be considered as a dication synthon. A plausible mechanism for the cross coupling reaction of this sulfur moiety is summarized in Scheme 1.

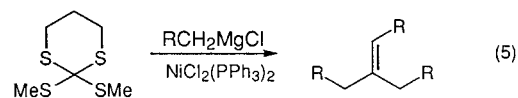


Scheme 1

Oxidative addition of one of the carbon-sulfur bonds with the nickel catalyst, association of the Grignard reagent to the nickel catalyst followed by a reductive elimination process form the basis for the first carbon-carbon bond formation. Various evidence suggests that the formation of carbon-carbon bond precedes the elimination step in these reactions.<sup>7</sup> The high reactivity found in benzylic dithioacetals versus low activity observed for benzylic thiols or thioethers<sup>5-8</sup> in the cross coupling reactions illustrates that the overall reaction is a tandem cascade process. The benzylic carbon-sulfur bond in intermediate thioether is activated because of the chelation with the terminal thiolato moiety. A model study confirms that intermediate **1** with appropriate chain length does proceed the oxidative addition with the nickel catalyst followed by  $\beta$ -hydride elimination readily at room temperature (eq 4).<sup>9</sup>

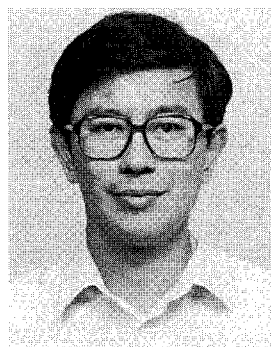
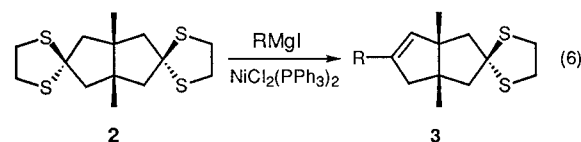


Simple aliphatic substrates are relatively unreactive towards the transition metal-catalyzed cross coupling reaction. Under these conditions, only primary aliphatic iodides can undergo the cross coupling reaction with the main group organometallic reagents.<sup>10</sup> Side reactions such as elimination, reduction, or dimerization occasionally occur.<sup>11</sup> Like most other aliphatic substrates, a dithioacetal group without an aryl or a vinyl activating group does not undergo cross coupling reactions.<sup>6-8</sup> The major obstruction may arise from the low reactivity of these C-S bonds in the oxidative addition process. The bond strength may play a significant role in these reactions. Interestingly, the carbon-sulfur bonds in trithioorthoesters or tetrathioorthocarbonate, which are relatively weak, have been found to undergo the cross coupling reactions in the presence of a nickel catalyst (eq 5).<sup>12</sup> A mechanism similar to that described in Scheme 1 should also apply here. In other words, as soon as the first carbon-sulfur bond is activated, the following steps involving the reactions of the remaining carbon-sulfur bonds would occur rapidly, even an aliphatic C-S bond being activated. In other words, the involvement of a chelation intermediate similar to **1** would enhance the overall reactivity. Such strategy may also assist the cleavage of the aliphatic C-S bond leading to the cross coupling reactions.



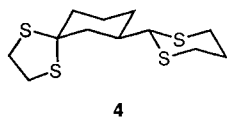
## 2.2. Prototype<sup>13</sup>

An initial effort has been made to focus on the nickel-catalyzed cross coupling reactions of certain rigid bisdithioacetals. The two endo sulfur moieties in **2** are located in proximity and therefore can symbiotically interact with the nickel catalyst. As such, one of these two dithioacetal moieties can undergo the cascade cross coupling reaction leading to the corresponding olefination product **3** (eq 6). The remaining dithioacetal group is intact because it is no longer activated. This reaction can be considered as a selective modification of one of the two carbonyl equivalents.

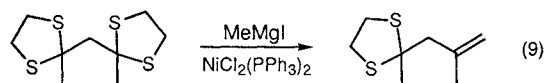
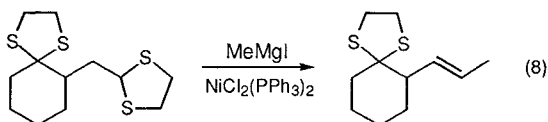
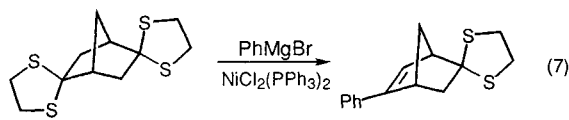


Tien-Yau Luh received his B.S. degree from National Taiwan University and his Ph.D. degree from the University of Chicago (with L. M. Stock). After spending two years as a postdoctoral associate at the University of Minnesota (with P. G. Gassman), he joined the Chinese University of Hong Kong in 1976 and returned to his alma mater in 1988, where he is currently Professor of Chemistry. His current research interests include development of new synthetic methods using organometallic reagents, carbohydrate chemistry and chemistry of materials.

The criterion for the success of these transformations depends on the ability of the two sulfur moieties coordinating simultaneously to the nickel-catalyst. Substrates such as **4**, which are unable to form chelation with the nickel catalyst, do not react under these reaction conditions.

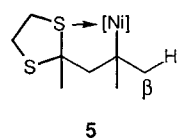


The most commonly used nickel catalyst in these reactions is  $\text{NiCl}_2(\text{PPh}_3)_2$ , although complexes having bidentate ligands such as dppf or the like behave similarly. Bis(dithioacetals) derived from cyclic or acyclic diketones yield the corresponding monoolefination products. Methyl, silylmethyl as well as aryl Grignard reagents react smoothly with bis(dithioacetals). Representative examples are shown in eqs 7-9.

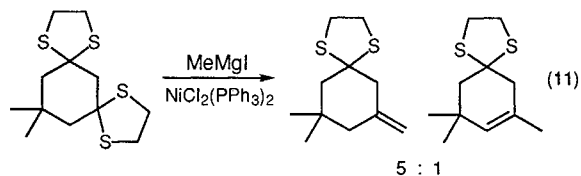
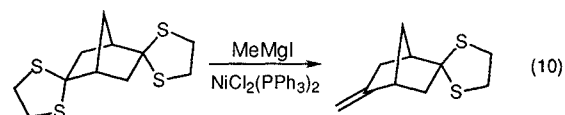


### 2.3. Regioselectivity<sup>13</sup>

When bis(dithioacetals) derived from 1,3-diketones are used, homoallylic dithioacetals are isolated selectively (eqs 6 and 9). Apparently, a possible chelate intermediate **5** may determine the orientation of the  $\beta$ -hydride elimination preferentially leading to the formation of the corresponding homoallylic dithioacetals.

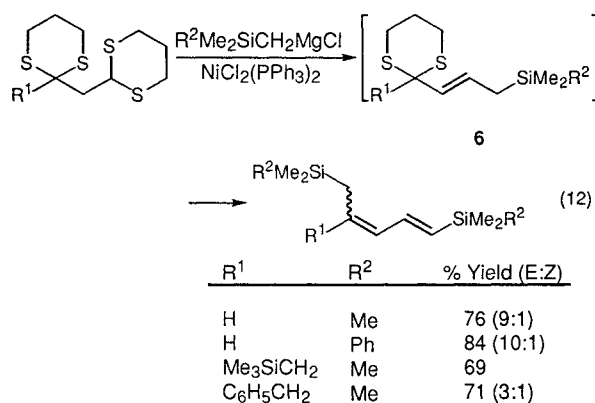


The selectivity for the formation of the double bond in bis(dithioacetals) derived from 1,4- or 1,5-diketones depends on the nature of the substrates. No intermediate like **5** would be expected from these reactions because the remaining sulfur atom would be too far away from the nickel center for coordination. Consequently, the orientation of the double bond formation would depend on the relative stability of the product or on the availability of the cis-coplanar  $\beta$ -hydrogen. Thus, five-membered-ring substrates give the products having endocyclic double bond predominantly, if not exclusively (eq 6). However, the relatively less strained exocyclic methylene-norbornane derivative is isolated as the sole product from the reaction of more strained substrate (eq 10). Six-membered ring substrates are less selective, an isomeric mixture of endo- and exocyclic double bonds is usually obtained (eq 11).

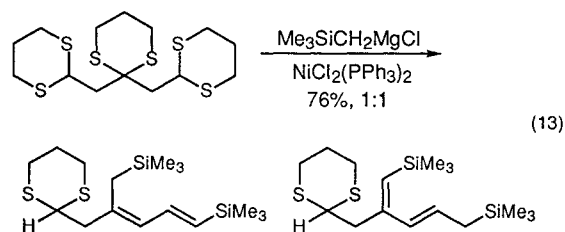


### 2.4. Tandem Cross Coupling Reactions<sup>13</sup>

The reactions with less rigid acyclic 1,3-bisdithioacetals are interesting. Bis(dithioketals) behave just like the cyclic substrates, giving homoallylic dithioacetals (eq 9). On the other hand, when one of these two sulfur heterocycles is derived from an aldehyde group, the selectivity changes. Thus, 1,3-bisdithianes react with  $\text{RMe}_2\text{SiCH}_2\text{MgCl}$  ( $\text{R} = \text{Me}$  and  $\text{Ph}$ ) under the similar conditions afford the corresponding silyl-substituted dienes in good yields (eq 12).<sup>14</sup> Presumably, an allylic dithioacetal intermediate **6** is involved. Further coupling with the Grignard reagent leads to the diene products.

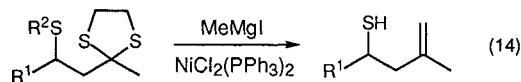


Interestingly, only two sulfur heterocycles of trisdithiane undergo cross coupling reaction and the third dithiane ring, which is homoallylic in nature, remains intact (eq 13).



### 2.5. Reactions of Thioether-Dithioacetals<sup>13</sup>

The extension of the cross couplings to thioether-dithioacetals gives regioselectively homoallylic thiols (eq 14). Ethylene ( $\text{R}^2 = \text{HSCH}_2\text{CH}_2$ ) is also obtained by fragmentation of the carbon fragments in the thioether linkage by oxidative addition across a C-S bond followed by  $\beta$ -sulfur elimination.

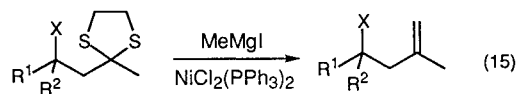


$\text{R}^1 = \text{alkyl}$  or  $\text{H}$ ;  $\text{R}^2 = \text{H, Alkyl, HS(CH}_2)_2$ -

The regioselective formation of the double bond can be understood within the same framework described earlier via an intermediate similar to **5**. No reaction has been observed when these substrates are treated with the Grignard reagent in the absence of a nickel catalyst.

## 2.6. Other Heteroatom-Assisted Olefination of Dithioacetals<sup>13</sup>

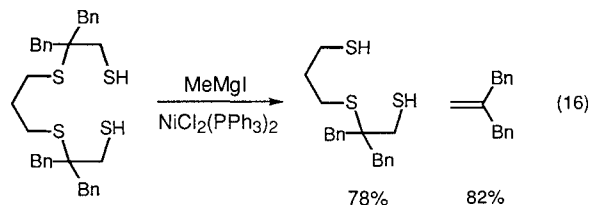
Other heteroatom substituents such as hydroxy, methoxy or amino groups also assist the alkenation of aliphatic dithioacetals; and homoallylic alcohols, ethers and amines are obtained, respectively, in reasonably good yields (eq 15). Similar to sulfur analogs, when the heteroatom substituent is located at the  $\beta$ -position, the double bond is also formed regioselectively. Again, an intermediate like **5** where the sulfur moiety is replaced by a heteroatom group may be involved. This procedure provides an interesting route for the preparation of homoallylic alcohols, ethers, thiols as well as amines.



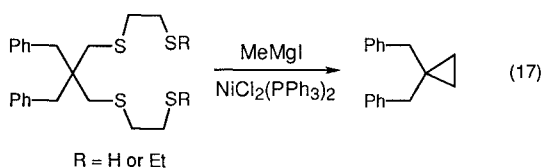
$R^1, R^2 = \text{alkyl or H}; X = \text{OH, OMe, NMe}_2$

## 2.7. Reactions of Polythioethers with Grignard Reagents<sup>13</sup>

In the previous section, we have discussed the different behavior of aliphatic thioether and dithioacetal functionalities under the conditions of the nickel-catalyzed reaction with Grignard reagents. The dithioacetal group undergoes the normal olefination reaction, whereas fragmentation is observed with the thioether functionalities. The application of the latter reaction to a polythioether under similar conditions as described above affords a  $1,\omega$ -dimercapto-thioether in good yields (eq 16). In addition, an olefinic product is isolated in 82% yield.



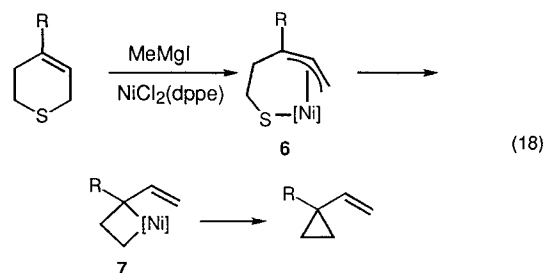
Under more vigorous conditions or higher concentration of the nickel catalyst,  $1,\omega$ -dimercaptothioethers are converted into cyclopropane derivatives. Due to the symbiotic interaction of the sulfur moieties with the nickel catalyst, all C-S bonds are cleaved giving a nickelacyclobutane intermediate which undergoes reductive elimination to generate the corresponding cyclopropane product.



$R = \text{H or Et}$

## 2.8. Desulfurative Coupling of Thiapyrans<sup>13</sup>

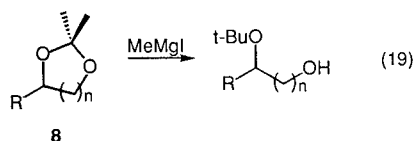
Aside from heteroatoms, as discussed in the previous section, which can play a unique role in the activation of the carbon-sulfur bonds under the nickel-catalyzed cross coupling reaction conditions, a  $\pi$ -allyl complex could also assist in the cleavage of the chelated carbon-sulfur bond. Thus, 5,6-dihydro-2H-thiapyran may serve as a useful model because it has two different kinds of carbon-sulfur bonds, one being allylic and the other aliphatic. The oxidative addition with the nickel catalyst occurs readily at the allylic C-S bond to give possibly the sulfur-coordinated  $\pi$ -allyl intermediate **6**. The remaining C-S bond may be activated owing to chelation and undergoes further cleavage leading to an organonickel intermediate **7** which will undergo reductive elimination to give the corresponding vinylcyclopropane (eq 18).



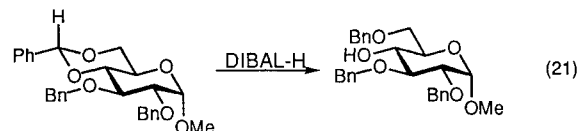
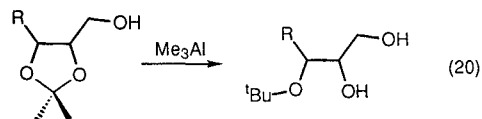
## 3. Regioselective C-O Bond Cleavage Reactions

### 3.1. Prototype

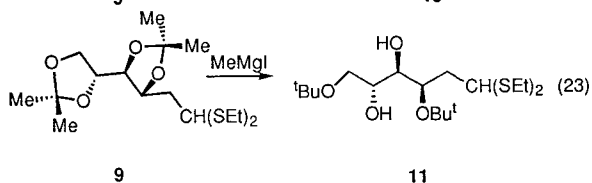
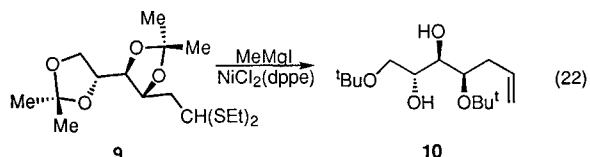
Selective transformation of an acetal of a contiguous diol into the corresponding hydroxyalkyl ether would be highly useful in synthesis because the two hydroxyl groups can thus be differentiated. Thus, the reaction of a Grignard reagent or other carbon nucleophiles with an acetal has been known for almost three decades.<sup>15</sup> The investigations on the diastereoselective ring opening reactions of acetals under various conditions have been extensive. However, it was not until recently that the regioselective coupling reactions of acetals with carbon nucleophiles become more useful. Thus, acetals **8** undergo regioselective cleavage reactions with the Grignard reagent in refluxing benzene, giving the corresponding hydroxyalkyl ethers (eq 19).<sup>16</sup> Both five- and six-membered acetonides behave similarly and the C-O bond of the less hindered site in **8** is cleaved regioselectively. Presumably, the oxygen atom on this site would coordinate to magnesium preferentially, resulting in the regioselective protection of the more hindered hydroxy group of a diol.



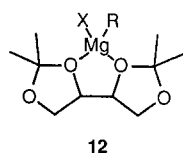
As discussed in the previous sections, chelation demonstrates a powerful arsenal for the regioselective cross coupling of aliphatic dithioacetals with Grignard reagents. Indeed, chelation has also been found useful for the selective reaction of an acetal having a neighboring hydroxy group with trimethylaluminum to afford regioselectively the corresponding alkoxydiol (eq 20).<sup>17</sup> However, the selectivity becomes unsatisfactory when the hydroxy group is replaced by an alkoxy moiety. Regioselective reduction of 1,2-O-benzylidene derivatives of certain carbohydrates with DIBAL-H has been reported (eq 21).<sup>18</sup> However, a mixture of regioisomers is occasionally obtained.



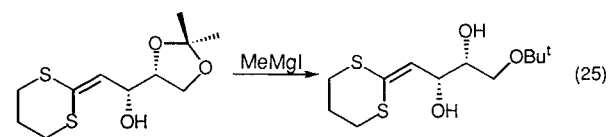
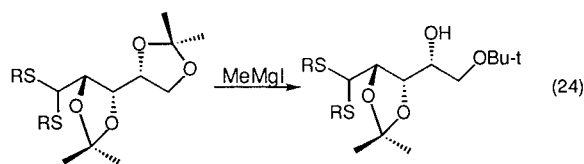
In the previous section, we have demonstrated that the aliphatic dithioacetal group is activated to undergo the olefination reaction owing to the presence of a neighboring heteroatom which may from chelate with the nickel catalyst. This strategy has been extended to a sugar derivative **9** (eq 22).<sup>13b,16</sup> In the presence of the nickel catalyst, the oxygen-atom assisted olefination coupled with the regioselective ring opening of both acetonide moieties occurs to give **10**. When the nickel catalyst is absent, **11** is obtained and the carbon-sulfur bonds remain intact (eq 23).



Two interesting features can be concluded from these preliminary experiments. Firstly, when the nickel catalyst is used, it will symbiotically interact with the sulfur atom and the neighboring oxygen atom leading to the olefination reaction. In addition, the magnesium will form chelation with the oxygen atoms from both acetal groups (e.g. **12**) resulting in the regioselective cleavage of the C-O bonds.



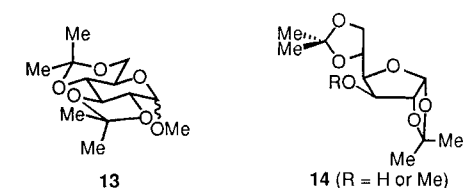
The monohydroxy derivative can be obtained selectively under mild conditions (60 °C) as shown in eq 24. It is noteworthy that the hydroxy group can also direct the cleavage reaction selectively (eq 25).



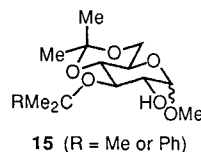
### 3.2. Monosaccharide Derivatives Having One Free Hydroxy Group<sup>19</sup>

The acetal functionality is one of the most useful protective groups for diols in general and for carbohydrate derivatives in particular.<sup>19</sup> Based on the chelation strategy depicted above, acetonides can be cleaved regioselectively with Grignard reagents when a neighboring hydroxy or alkoxy group is present.<sup>13b</sup> Accordingly, selective cleavage of one of the two C-O bonds in the acetal-protected monosaccharides will offer a powerful arsenal for the selective synthesis of various monosaccharide derivatives having *only* one free hydroxyl group.

The two readily accessible glucose bisacetonides **13** and **14** have been used to test the generality of the reaction. Treatment of **13** with Grignard reagents in benzene-ether yields **15** exclusively. Interestingly, both anomeric  $\alpha$ - and  $\beta$ -methoxy groups in **13** give the same cleavage pattern, liberating the 2-hydroxy derivatives **15** in good to excellent yields. The chelation of OMe group and the neighboring oxygen function at C<sub>2</sub> with magnesium may account for the results. When **13** ( $\alpha$ -OMe) is treated with MeMgI under refluxing toluene conditions, diol **16** is isolated in 71% yield.

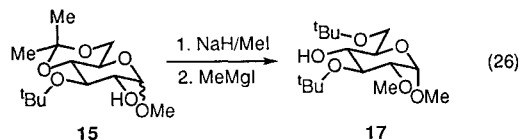


14 (R = H or Me)

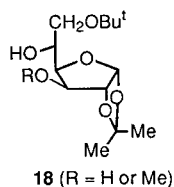


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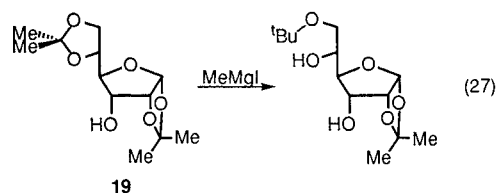
Methylation of **15** with MeI/NaH followed by treatment with MeMgI gives the corresponding 4-OH derivative **17** (eq 26).



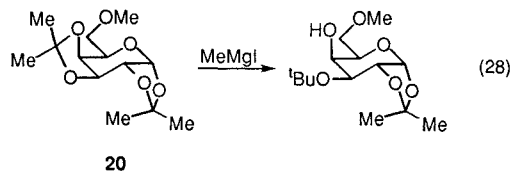
The reaction of **14** (R = H) under the same conditions yields **18** (R = H) which has hydroxy groups at C<sub>3</sub> and C<sub>5</sub> positions. In a similar manner, treatment of **14** (R = Me) with MeMgI gives **18** (R = Me) exclusively in 68% yield.



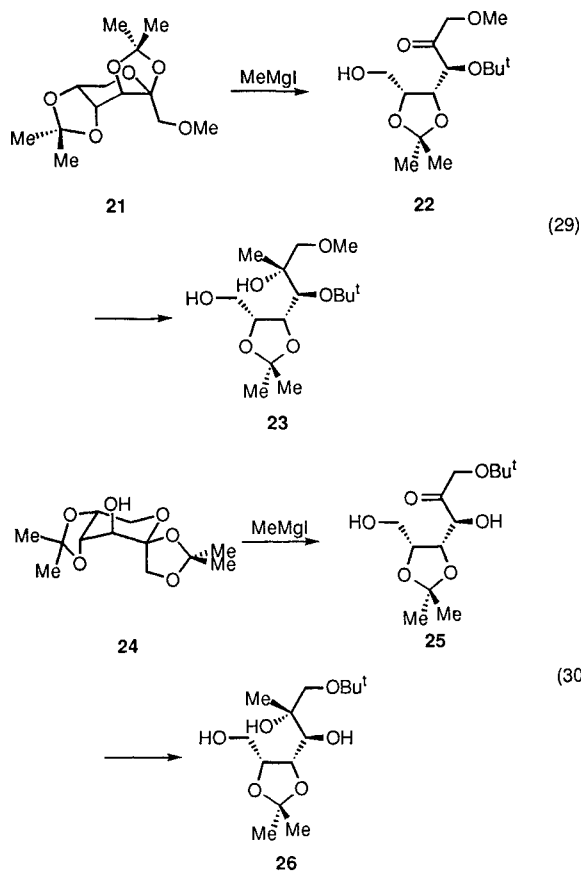
The presence of a  $\beta$ -hydroxy or  $\beta$ -methoxy group at C<sub>3</sub> in **14** is not essential for the selectivity of this ring-opening process. The reaction of allose derivative **19** also affords the corresponding 5-OH product (eq 27). Accordingly, the chelation with the oxygen atom on the five-membered heterocycle may determine the selectivity in these reactions.



The reaction with galactose derivative **20** furnishes the corresponding 4-hydroxy derivative (eq 28). Apparently, the chelation with the methoxy group at C<sub>6</sub> controls the regioselectivity.

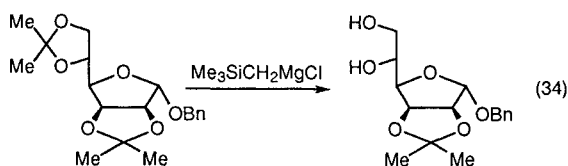
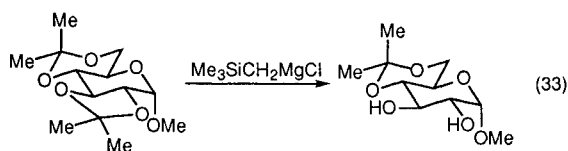
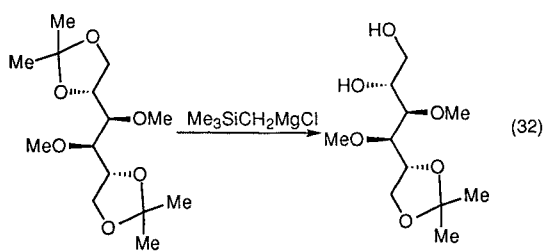
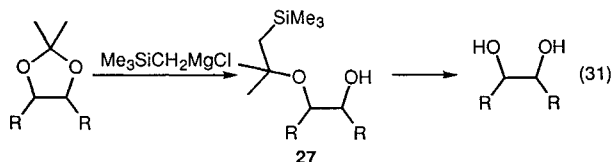


The reactions involving fructose derivatives also behave similarly. Thus, treatment of **21** with MeMgI under usual conditions gives **23** selectively. The methoxy group at C<sub>1</sub> would assist the cleavage reaction to occur at C<sub>2</sub> giving a ketone intermediate **22** which further reacts with MeMgI stereoselectively to yield **23** (eq 29). In a similar manner, the hydroxy group at C<sub>3</sub> in **24** also aids the regioselective ring-opening of the acetonide at C<sub>2</sub> to afford **26** via **25** (eq 30).



### 3.3. Selective Deprotection of Acetonides to Liberate Diols<sup>20</sup>

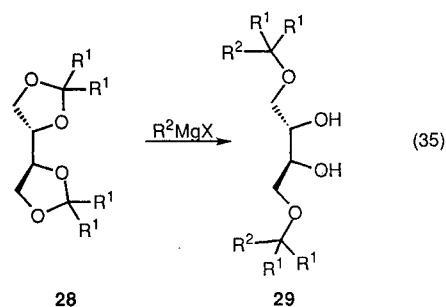
The trimethylsilylethyl group is a useful protective group for alcohols and can be removed easily by treatment with  $\text{BF}_3$ .<sup>21</sup> Thus, the



reaction of an acetonide with  $\text{Me}_3\text{SiCH}_2\text{MgCl}$  would lead to a  $\omega$ -silyl-substituted *tert*-butoxy alkanol **27**. Surprisingly, only diol is isolated (eq 31). Hence, this transformation can be considered as an unprecedented procedure for the regioselective deprotection of a ketal group under basic conditions. As discussed in the previous sections, chelation can cleave the ketal regioselectively. By combining these two strategies, selective deprotection of ketals can be achieved (eq 32-34).

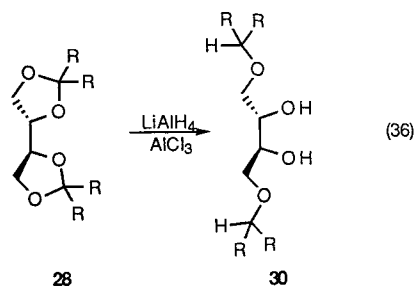
### 3.4. Synthesis of Tunable $\text{C}_2$ -Chiral 1,2-Diols

As shown in eqs 22 and 23, the reactions of a neighboring bisacetonide with  $\text{MeMgI}$  afford the corresponding diols regioselectively. This methodology can be used for the synthesis of various tunable  $\text{C}_2$ -chiral diols. Thus, 1,4-di-*tert*-alkoxy-(2*S*,3*S*)-2,3-butanediols **29** ( $\text{R}^2 = \text{alkyl}$ ) are easily accessible from the corresponding *L*-tartaric acid-based bisketals **28** (eq 35).<sup>22,23</sup> The size of the *tert*-alkoxy substituent can easily be tuned by varying the ketal group ( $\text{R}^1$ ) or by changing the Grignard reagent ( $\text{R}^2$ ).



$\text{R}^1$	$\text{R}^2$	%Yield
Me	Me	89
Me	Et	77
Me	<i>i</i> -Pr	64
Me	$\text{PhCH}_2$	60
Et	Me	85
$\text{R}^1\text{R}^1$ c-C <sub>4</sub> H <sub>8</sub>	Me	70
$\text{R}^1\text{R}^1$ c-C <sub>5</sub> H <sub>10</sub>	Me	70

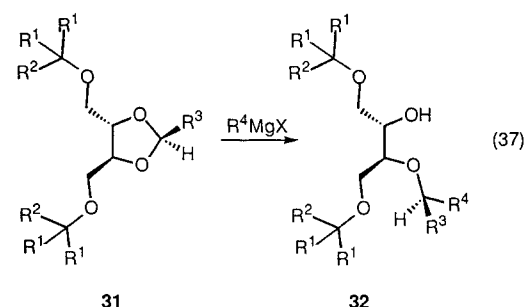
It is known that acetals can undergo reductive cleavage with  $\text{LiAlH}_4$ - $\text{AlCl}_3$ .<sup>24</sup> Aluminum can form chelation complexes with heteroatoms.<sup>25</sup> Accordingly, similar to **12**, complexation with the aluminum reagent would be anticipated when bisacetals **28** are employed. Reductive cleavage of the acetal moiety in **28** with  $\text{LiAlH}_4$  in the presence of a catalytic amount  $\text{AlCl}_3$  leads to 1,4-bis-*sec*-alkoxybutane-2,3-diol **30** (eq 36).<sup>26</sup>



$\text{R}$	%Yield
Me	58
Et	77
$\text{R R}$ c-C <sub>4</sub> H <sub>8</sub>	64
$\text{R R}$ c-C <sub>5</sub> H <sub>10</sub>	60

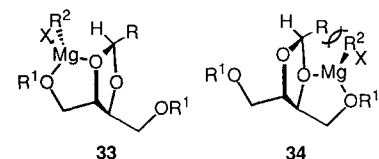
### 3.5. Diastereoselective Ring-Opening Reactions of Chiral Acetals with Grignard Reagents<sup>22</sup>

Diols **29** and **30** might be useful to serve as an auxiliary in asymmetric synthesis because the size of the alkoxy substituents can be tuned. Besides, the oxygen atom in the alkoxy substituent can act as an additional ligand for complexation with the metallic species which would enhance the stereoselectivity of the reaction. This advantage has been tested by investigating the diastereoselective ring-opening reactions of chiral acetals **31** with Grignard reagents (eq 37). Interestingly, only sterically hindered or secondary cyclic Grignard reagents give excellent diastereoselectivity whereas MeMgI gives poor selectivity.

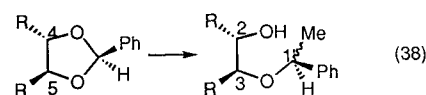


R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	%Yield	de %
Me	Me	Ph	c-C <sub>5</sub> H <sub>9</sub>	83	96
Me	Me	p-PhC <sub>6</sub> H <sub>4</sub>	c-C <sub>5</sub> H <sub>9</sub>	84	95
Me	i-Pr	p-PhC <sub>6</sub> H <sub>4</sub>	c-C <sub>5</sub> H <sub>9</sub>	78	96
Me	Me	p-BrC <sub>6</sub> H <sub>4</sub>	c-C <sub>5</sub> H <sub>9</sub>	77	95
Me	Me	m-MeOC <sub>6</sub> H <sub>4</sub>	c-C <sub>6</sub> H <sub>11</sub>	80	98
Me	Me	Ph	c-C <sub>6</sub> H <sub>11</sub>	84	98
Me	Me	m-MeOC <sub>6</sub> H <sub>4</sub>	Ph	73	98
Me	Me	m-MeOC <sub>6</sub> H <sub>4</sub>	Me <sub>3</sub> CCH <sub>2</sub>	81	94

Several interesting features about the ring-opening reactions with the Grignard reagent are noteworthy. These results provide the first example on the highly diastereoselective ring-opening of chiral acetals using sterically bulky or secondary Grignard reagents. It seems likely that, with bulky Grignard reagent, intermediate **33** would be more stable than **34**. Although the actual mode of the ring-opening reaction of acetals is not clear, retentive displacement of the C-O bond by an alkyl group from intermediate **33** is speculated.



Interestingly, the diastereoselectivities for the reactions of **31** with MeMgI in the presence and in the absence of TiCl<sub>2</sub>(OPr<sup>i</sup>)<sub>2</sub> are opposite (eq 38). The selectivity of such titanium-promoted reaction parallels to those in the other substrates using similar conditions.<sup>27</sup>



R	Reagent	%Yield	R/S at C <sub>1</sub>
<sup>t</sup> BuOCH <sub>2</sub> ( <b>31</b> )	MeMgI	83	0.6
<sup>t</sup> BuOCH <sub>2</sub> ( <b>31</b> )	MeMgI, TiCl <sub>2</sub> (OPr <sup>i</sup> ) <sub>2</sub>	71	2.3
Me ( <b>35</b> )	MeMgI	82	1.8

Presumably, the titanium reagent competes with the Grignard reagent for complexation resulting in the invertive ring cleavage.<sup>22</sup>

In order to clarify the validity of this conjecture, the reaction of (4*S*,5*S*)-**35**, which does not have the oxygen atom on the side chain for chelation, with MeMgI under similar conditions gives the corresponding product in a 82% yield with 30%de in favor of *R*-configuration at C<sub>1</sub> position. The selectivity is just opposite to that observed for the reactions of **31**. This discrepancy suggests that the chelation intermediate **33** may be involved in the reaction of **31** with Grignard reagents leading to the retentive displacement of a C-O bond by a C-C bond.

### 4. Conclusions

Acetals and dithioacetals are traditionally used as the carbonyl protective groups.<sup>21</sup> The chemistry described herein provides new entries in the synthetic use of these functionalities. With the aid of a nickel catalyst, the otherwise unreactive carbon-sulfur bonds in aliphatic dithioacetals as well as other organosulfur compounds of different structural variety are readily replaced by carbon-carbon bonds. The regioselective cleavage of the C-O bonds in acetals can pave the way to make predictions of other opportunities for new applications, in particular, in carbohydrate chemistry. Room emanating from the present research abounds.

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