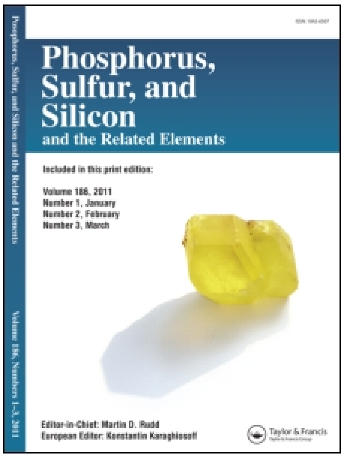

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Chelation Assisted Conversion of C-S Bonds into C-C Bonds

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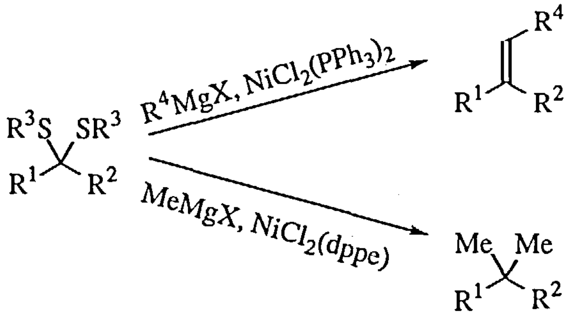
When substrates contain more than two proximal heteroatoms which can interact *symbiotically* with a metallic species, one of these carbon-heteroatom bonds can be activated. This strategy has been applied for the nickel-catalyzed cross coupling reactions of certain rigid bisdithioacetals. Heteroatom substituents such as hydroxy, methoxy or amino groups also assist the alkenation of aliphatic dithioacetals; and homoallylic alcohols, ethers and amines are respectively obtained in reasonably good yields Polythioethers are converted into cyclopropane derivatives.

INTRODUCTION

Transition metal-catalyzed cross-coupling reactions are useful to convert a carbon-sulfur bond to the corresponding carbon-carbon bond (eq 1).[1-3] The carbon-sulfur

$$\text{RSR'} \xrightarrow[\text{NiCl}_2(\text{PPH}_3)_2]{\text{R''M}} \text{R-R''} \qquad (1)$$

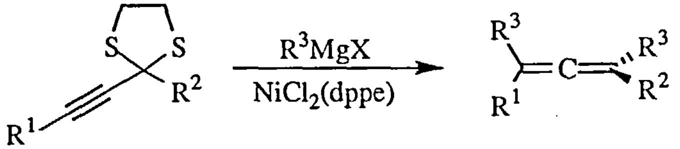
bond in these substrates has to be allylic, aryl, or vinylic; and simple aliphatic organosulfur compounds are unreactive. The extension of this cross-coupling reaction to benzylic or allylic dithioacetals has led to the discovery of two new types of transformations (Scheme 1).[4-7] In the first instance, one of the carbon-sulfur bonds is



SCHEME 1

substituted by a carbon-carbon bond, and subsequently the second carbon-sulfur bond is eliminated to produce an olefin.[8-13] The second type of the transformation involves the replacement of both carbon-sulfur bonds by carbon-carbon bonds which results in geminal dialkylation.[14-16] In these reactions, dithioacetals can be considered as geminal dication synthons.[6,7]

Under similar conditions, the propargylic dithioacetals react with the Grignard reagent to afford the corresponding allenes in excellent yield (eq 2). In this regard, the propargylic dithioacetal can be viewed as an allene 1,3-dication synthon.[17] Representative examples are tabulated in Table I.



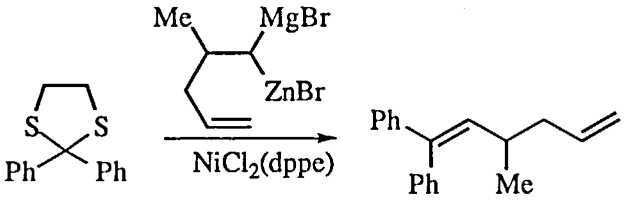
2)

TABLE I

NiCl$_2$(dppe)-catalyzed cross coupling reactions of propargylic dithioacetals with Grignard reagents.

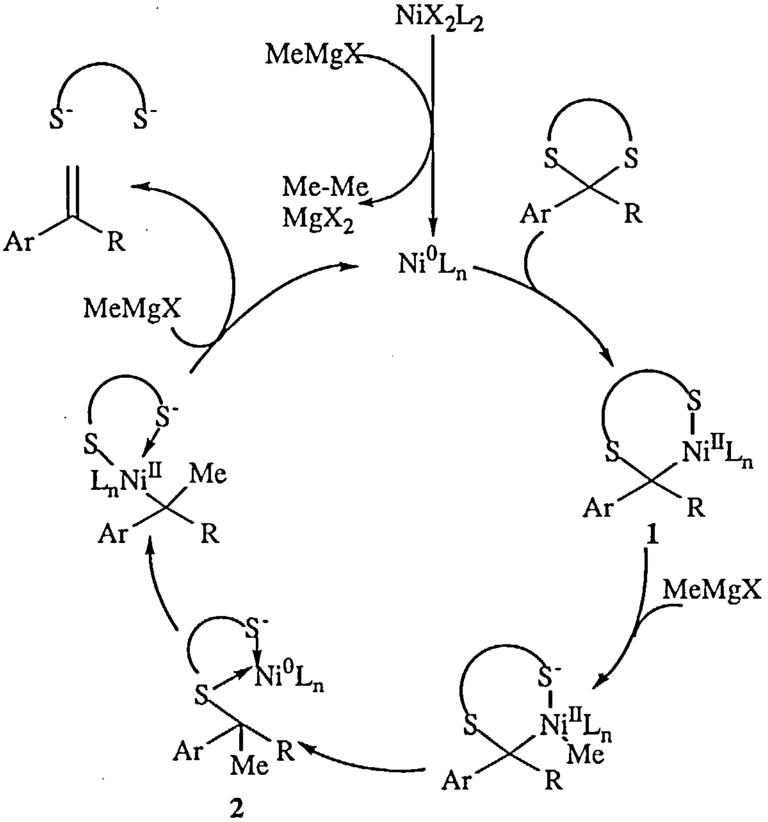
R^1	R^2	R^3	%Yield of allene
Ph	Me	Me	90
Ph	Ph	Me	79
Bu	Me	TMSCH$_2$	90
Ph	Me	TMSCH$_2$	92
TMS	Me	TMSCH$_2$	95
PhC≡C	Me	Me	78
Ph	Me	Ph	56

As just described, the dithioacetal group can be considered as a geminal dication synthon in the nickel-catalyzed cross-coupling reaction.[6,7] Accordingly, when a geminal bimetallic reagent is employed, the corresponding olefination product is envisaged (eq 3).[18]



(3)

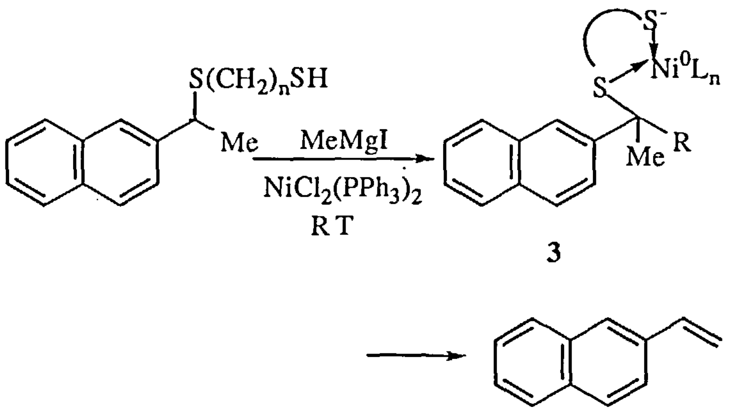
A possible catalytic cycle for the nickel-catalyzed cross coupling reaction of the benzylic dithioacetal is summarized in Scheme 2.[4-7] The most important feature in this catalytic reaction involves the formation of carbon-carbon bond before the elimination step.[8-18] Oxidative addition of one of the carbon-sulfur bonds in the dithioacetal group with the nickel catalyst will lead to an α-sulfur-substituted organonickel species **1** which may facilitate the carbon-carbon bond formation via an association of the Grignard reagent to the nickel catalyst, followed by reductive elimination. The high reactivity found in benzylic dithioacetals versus the low activity observed for benzylic thioethers[19,20] in the cross coupling reactions suggests that the



SCHEME 2

overall reaction is a cascade process. Because of the chelation with the terminal thiolato moiety, the benzylic carbon-sulfur bond in intermediate thioether **2** is activated. Attempts to isolate the possible intermediate(s), however, were unsuccessful.

A model study confirms that intermediate **3** with an appropriate chain length undergoes the oxidative addition with the nickel catalyst, followed by β-hydride elimination readily at room temperature (eq 4).[21] Because of the coordination of the ω-mercaptide anion, the nickel center in **2** or **3** is electron rich. Consequently, *the oxidative addition of the proximal carbon-sulfur bond would be very facile.*



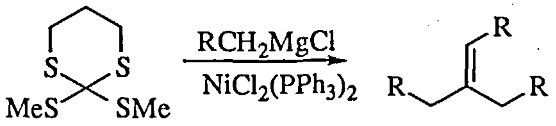
(4)

CROSS COUPLINGS OF ALIPHATIC DITHIOACETALS

Background

There have been limited cases where alkyl iodides can undergo the transition metal-catalyzed cross-coupling reaction.[22-25] To illustrate, neopentyl iodides react with aryl Grignard reagents in the presence of the $NiCl_2(dppf)$ catalyst.[22-24] In addition, primary alkyl iodides have been found to couple with an organoboron reagent under Suzuki reaction conditions.[25] Other substrates, however, undergo various side reactions such as reduction or dimerization via a radical intermediate or β-hydride elimination that leads to olefin formation.

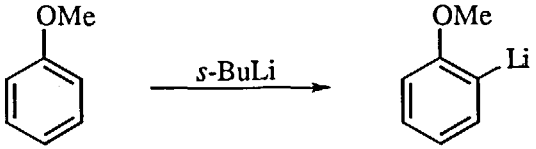
As expected, aliphatic dithioacetals remain intact under the cross-coupling conditions. The major obstacle may arise from the low reactivity of the C-S bond in the oxidative addition process. We recently found that the more reactive tetrathioorthocarbonate yields the corresponding coupling products under the nickel-catalyzed cross coupling conditions (eq 5).[26,27] This observation again indicates that the displacements of the carbon-sulfur bonds in tetrathioorthocarbonate occur similarly via a cascade process. 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 readily.



(5)

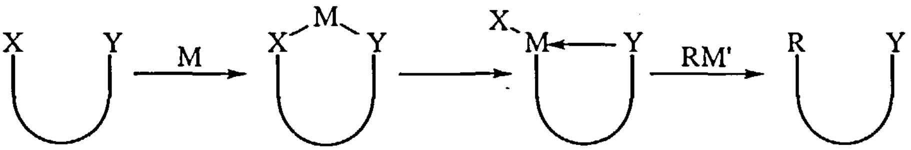
Chelation Strategy

Chelation plays an important role in directing the regio- and/or stereoselective transformations in organic synthesis. Metallation of an otherwise unreactive C-H bond can be achieved readily in this way.[28-31] A representative example is shown in eq 6.



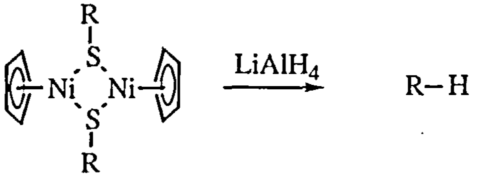
(6)

Relatively speaking, the use of this strategy to activate the carbon-heteroatom bonds has been rare. When substrates containing more than two proximal heteroatoms interact *symbiotically* with a metallic species, one of these carbon-heteroatom bonds can be activated (eq 7). 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 heteroatom, the properties of metallic species, the nature of substrates, and reaction conditions, selective transformation of a carbon-heteroatom bond to a carbon-carbon bond can be achieved.



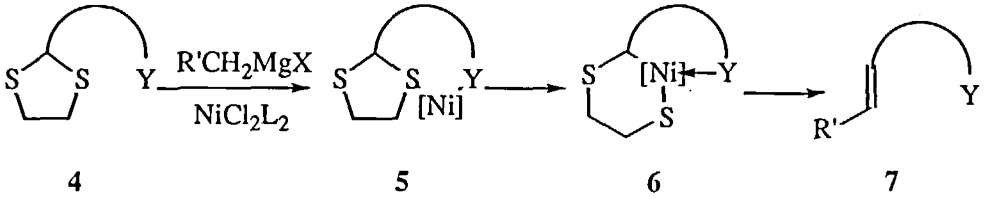
(7)

It is known the C-S bonds in certain complexes containing thiolato ligands are activated and the reduction of these C-S bonds to give the corresponding hydrocarbons can readily be achieved (eq 8).[32]



(8)

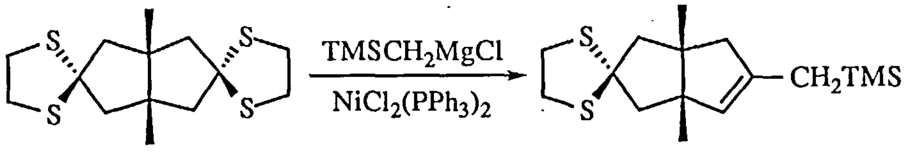
Polythioethers can readily form chelation complexes with transition metals.[33,34] Accordingly, such kind of complexation may assist the cleavage of the aliphatic C-S bond leading to the cross coupling reactions. Indeed, the reaction shown in eq 4 illustrates an intriguing example on the chelation-assisted activation of a benzylic carbon-sulfur bond leading to the elimination product.[21] It is envisaged that the aliphatic carbon-sulfur bond can also be activated if a similar complex is formed. Scheme 3 summarizes the strategy for the cross coupling reaction of the aliphatic dithioacetal. When a dithioacetal moiety 4 having other heteroatom(s) Y at a close proximal position, is treated with the Grignard reagent in the presence of a nickel catalyst, a chelation complex 5 would be expected. Nickel-catalyzed olefination of the dithioacetal moiety with the Grignard reagent might then occur leading to 7.



SCHEME 3

Cross Couplings of Bisdithioacetals

An initial effort has been made to focus on the nickel-catalyzed cross coupling reactions of certain rigid bisdithioacetals. For example, the two endo sulfur moieties in 8 are located in proximity and therefore can symbiotically interact with the nickel catalyst. Consequently, one of these two dithioacetal moieties is activated and undergoes the cascade cross coupling reaction leading to the corresponding olefination product 9 (eq 9). 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.[35-37]

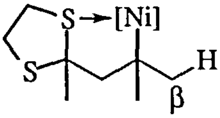


(9)

8 **9**

Other representative examples are shown in Table II.[35-37] The most commonly used nickel catalyst in these reactions is $NiCl_2(PPh_3)_2$, although complexes having bidentate ligands such as dppf or the like behave similarly. Methyl, silylmethyl as well as aryl Grignard reagents react smoothly with bisdithioacetals. The ring size of the dithioacetal moiety does not affect the product distributions; five-membered dithiolanes are, in general, more reactive than the six-membered analogs.

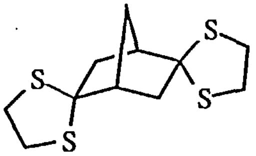
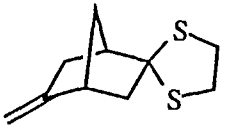
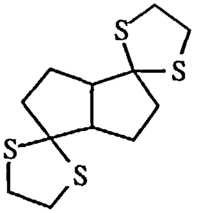
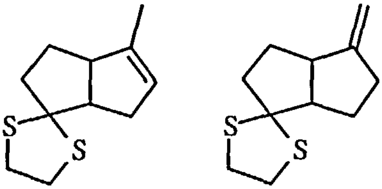
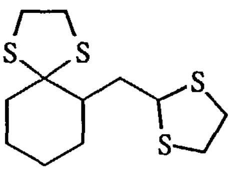
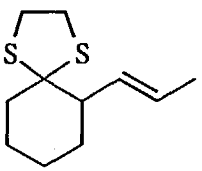
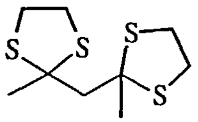
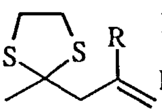
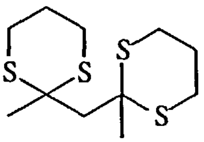
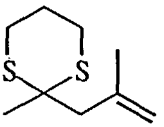
As can be seen from Table II, bisdithioacetals derived from cyclic or acyclic diketones yield the corresponding monoolefination products selectively. When bisdithioacetals derived from 1,3-diketones are used, homoallylic dithioacetals are isolated selectively (entries 5-7, Table II). A possible chelate intermediate **10** may determine the orientation of the β-hydride elimination preferentially leading to the formation of the corresponding homoallylic dithioacetals.



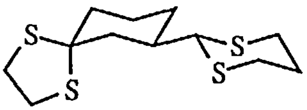
10

The selectivity for the formation of the double bond in bisdithioacetals derived from other diketones depends on the nature of the substrates. Since the remaining sulfur atom is quite remote from the nickel center for coordination, no intermediate like **10** would be expected from these reactions. Consequently, the orientation of the double bond formation would depend on the availability of the cis-coplanar β-hydrogen or on the relative stability of the product. Thus, five-membered-ring substrates give the products having endocyclic double bond predominantly, if not exclusively (entry 3, Table II). On the other hand, the relatively less strained exocyclic methylene-norbornane derivative is isolated as the sole product from the reaction of more strained substrate(entry 1, Table II). Six-membered ring substrates, however, are less selective, an isomeric mixture of endo- and exocyclic double bonds is usually obtained.[35,36]

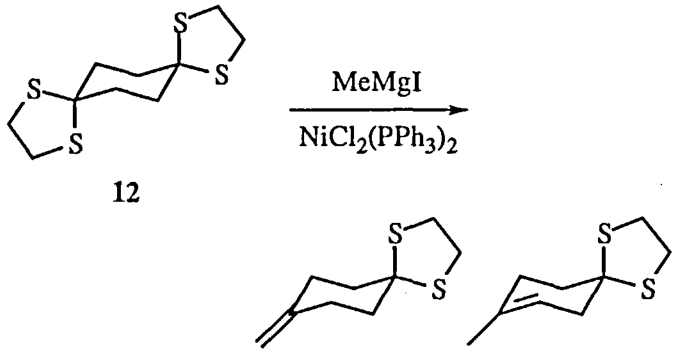
TABLE II
Chelation assisted nickel-catalyzed olefination of aliphatic dithioacetals

Entry	Substrate	Grignard reagent	Product	%Yield
1		MeMgI		78
2		PhMgBr		68
3		MeMgI	 8:1	72
4		MeMgI		76
5		MeMgI		R = Me, 72
6		$PhMe_2SiCH_2MgCl$		R = $PhMe_2SiCH_2$, 67
7		MeMgI		70

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 **11**, which are unable to form chelation with the nickel catalyst, do not react under these reaction conditions. In a similar manner, the reaction of **12** affords a mixture of the corresponding coupling products **13a** and **13b** in 18% yield, starting **12** being recovered in 75% yield (eq 10).[36]



11

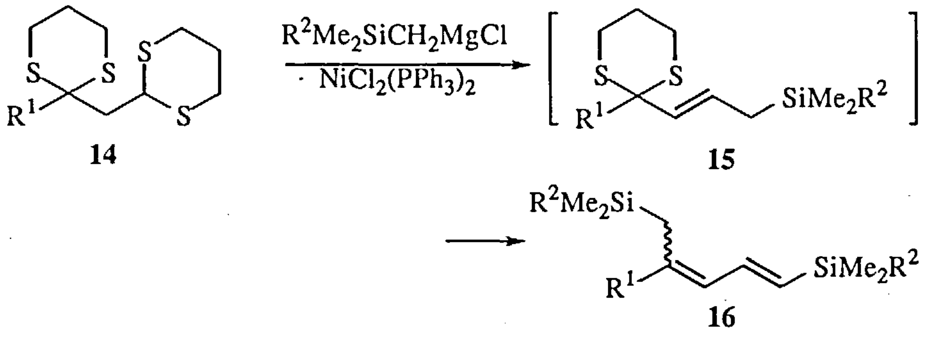


13a **13b**

(10)

Tandem Cross Coupling Reactions

The reactions with less rigid acyclic 1,3-bisdithioacetals are interesting. Bisdithioketals behave just like the cyclic substrates, giving homoallylic dithioketals (entries 5-7, Table II). On the other hand, when one of these two sulfur heterocycles is derived from an aldehyde group, the selectivity is very much dependent on the reaction conditions. When 1,3-bisdithianes **14** react with RMe_2SiCH_2MgCl (R = Me and Ph) in the presence of the nickel catalyst at low temperature (< 65°C), homoallylic dithioacetal is obtained in good yield.[38] On the other hand, when the reaction is carried out in refluxing benzene, the corresponding silyl-substituted dienes **16** in good yields (eq 11). Presumably, an allylic dithioacetal intermediate **15** is involved. Further coupling with the Grignard reagent leads to the diene products. Representative results are outlined in Table III.[36]

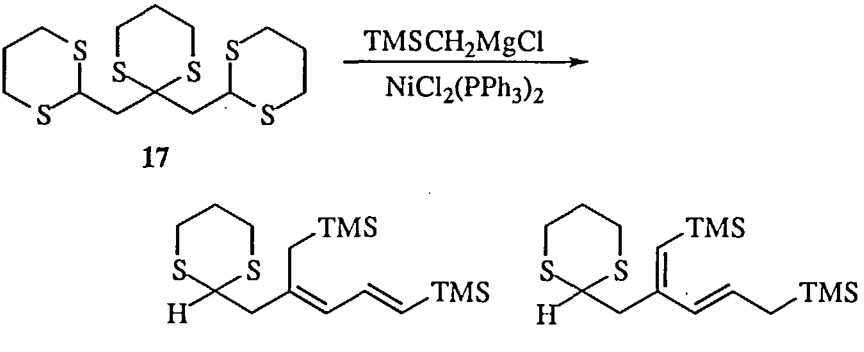


(11)

TABLE III
Nickel catalyzed reactions of **14** with $R^2Me_2SiCH_2MgCl$

R^1	R^2	%Yield of **16**
H	Me	76 (9:1)
H	Ph	84 (10:1)
$TMSCH_2$	Me	69
Bn	Me	71 (3:1)

Based on the similar strategy, when trisdithiane **17** is treated with $TMSCH_2MgCl$ under the same conditions, only two sulfur heterocycles undergo tandem cross coupling reaction to give a 1 : 1 mixture of **18** and **19** in 76% yield. It is noteworthy that the third dithiane ring, which is homoallylic in nature, remains intact (eq 12).

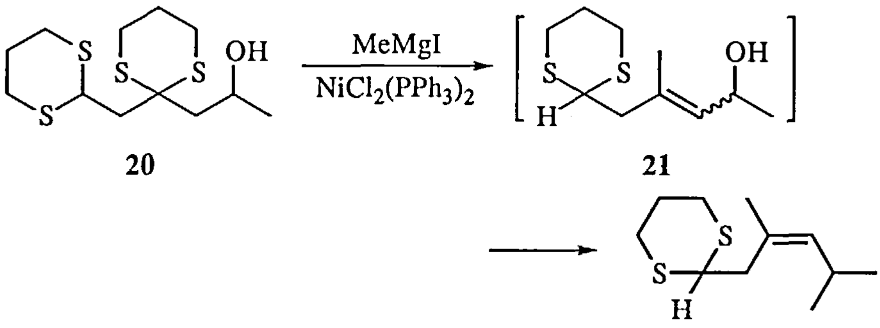


17

18 **19**

(12)

The nickel-catalyzed reaction of **20** with MeMgI interestingly yield the corresponding tandem coupling product **22** (eq 13). It is interesting to note that the "center" dithiane moiety may react first to give the allylic alcohol intermediate **21**. Presumably, both the terminal dithiane moiety and the oxygen atom will assist the



20

21

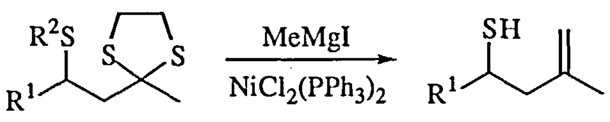
22

(13)

activation of the carbon-sulfur bond in the "center" heterocycle in this coupling reaction. The carbon-oxygen bond in **21** is then activated under these conditions and will undergo further coupling process to afford **22**.[38]

Reactions of Thioether-Dithioacetals

In the previous sections, the neighboring sulfur heterocycle has been shown to promote the coupling of the otherwise unactivated aliphatic dithioacetal moiety. The extension of this reaction to thioether-dithioacetals **23** gives selectively homoallylic thiols **24** (eq 14). Representative examples are outlined in Table IV.[36]

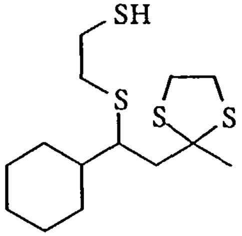
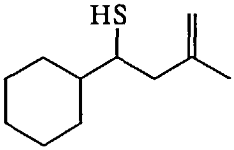
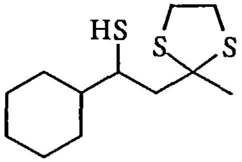
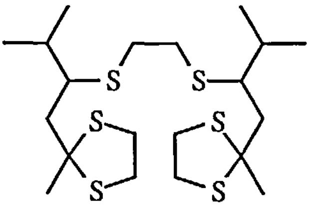
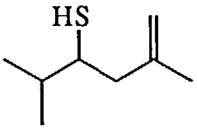
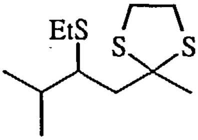


23 **24**

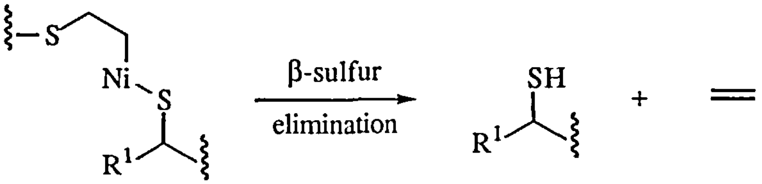
(14)

TABLE IV

$NiCl_2(PPh_3)_2$-catalyzed reactions of thioether-dithioacetals with MeMgI

substrate	product	%yield of 24
		70
		67
		65
		68

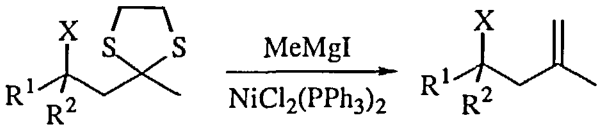
In these reactions, the carbon-sulfur bonds in both dithioacetal heterocycle and the thioether moiety are activated. Ethylene is obtained by fragmentation of the carbon fragments in the thioether linkage by oxidative addition across a C-S bond followed by β-sulfur elimination (eq 15).[39]



(15)

Oxygen and Nitrogen Atom-Assisted Olefination of Dithioacetals

In addition to sulfur moiety, hydroxy, alkoxy as well as amino groups can also serve as an auxiliary to assist the alkenation of aliphatic dithioacetals (eq 16, Table V). This procedure provides an interesting route for the preparation of homoallylic alcohols, ethers, thiols as well as amines.[36]



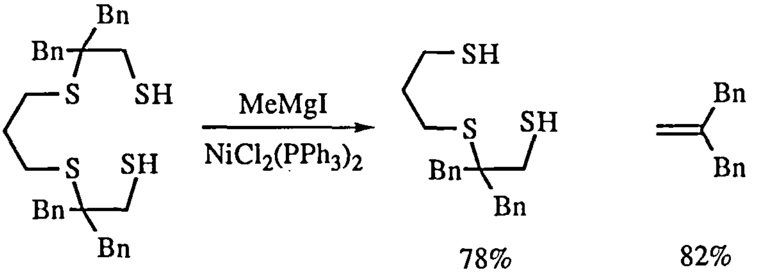
25 26 (16)

TABLE V
$NiCl_2(PPh_3)_2$-catalyzed reactions of thioether-dithioacetals with MeMgI

R^1	R^2	X	%Yield of **26**
$PhCH_2CH_2$	Me	OH	75
$PhCH_2CH_2$	Me	OMe	77
H	H	NEt_2	71

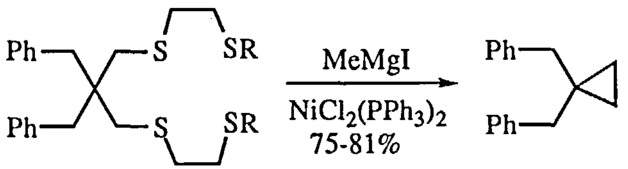
FRAGMENTATION OF ALIPHATIC POLYTHIOETHERS

As shown in eq 15, aliphatic thioether moiety undergoes fragmentation in the chelation-assisted nickel-catalyzed reaction with Grignard reagents. Thus, polythioethers are expected to undergo such degradation reaction leading to selectively chop one of the terminal mercaptoethyl group which will also give the corresponding alkenes (eq 17).[36]

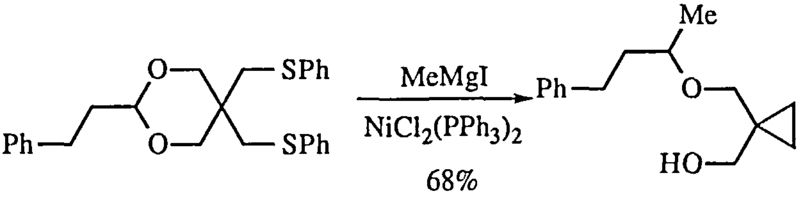


(17)

Under more vigorous conditions, exhaustive desulfurization will occur to give the cyclopropane derivatives (eq 18). Presumably a nickelacyclobutane intermediate is involved.[36] It is noteworthy that the carbon-oxygen bond in acetals also undergoes alkylative cleavage reaction (eq 19).[36,40]



(18)



(19)

DESULFURATIVE COUPLING OF DIHYDROTHIAPYRANS

Besides heteroatoms, as discussed in the previous section, which can play a key role in the activation of the carbon-sulfur bonds, a π-allyl complex can also assist in the cleavage of the chelated carbon-sulfur bond. Thus, treatment of **27** with the Grignard reagent under the nickel catalyzed conditions gives vinylcyclopropane **30** in good yield. The oxidative addition with the nickel catalyst may occurs readily at the allylic carbon-sulfur bond to give possibly the sulfur-coordinated π-allyl intermediate **28**. The remaining carbon-sulfur bond may then be activated due to chelation leading to an organonickel intermediate **29** which will undergo reductive elimination to form **30** (eq 20, Table VI).[36]

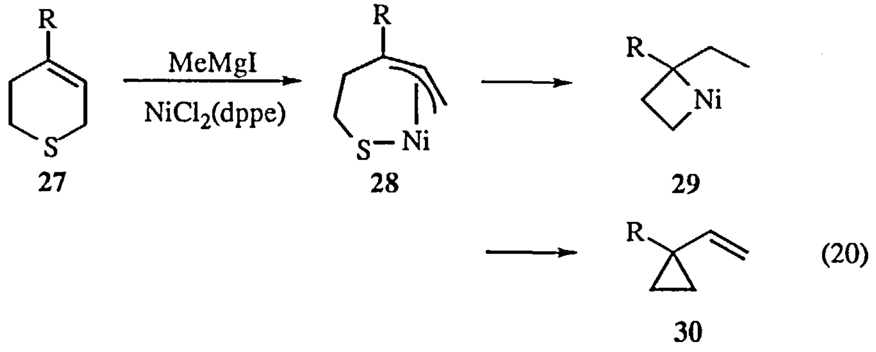


TABLE VI
Nickel-catalyzed reactions of 27 in the presence of MeMgI

R^1	%Yield of 30
Ph	81
4-MeC_6H_4	81
2-MeC_6H_4	81
4-$MeOC_6H_4$	81
$Ph(CH_2)_4$	81

CONCLUSIONS

The chemistry described herein provides a new entry in the activation of the otherwise unreactive carbon-sulfur bonds under the cross coupling conditions. Aliphatic dithioacetals having appropriate auxiliary heteroatoms can undergo selectively olefination reactions. Thioethers undergo the fragmentation reaction to give olefins or cyclopropanes. The strategy can pave the way to make predictions of other opportunities for new applications in the activation of the carbon-heteroatom bond by means of chelation.

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