Transition-Metal-Mediated C–S Bond Cleavage Reactions

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The transformations of carbon–sulfur bonds into carbon-hydrogen and carbon–carbon bonds under homogeneous conditions are discussed. The reduction methods using metal carbonyls, low-valent transition metal complexes, metal hydrides, Grignard reagents and transition metal compounds as reducing agents are presented. The reactions leading to the carbon–carbon bond formation by coupling with main group organometallic nucleophiles, desulfurdimerization, carbonylation and related methods are reviewed. Some other synthetically useful reactions involving the cleavage of carbon–sulfur bonds are also briefly discussed.

1. Introduction

Organosulfur compounds have played an important role in organic synthesis.[1–4] The sulfur moiety in most of these reactions serves as an auxiliary group and is normally removed afterwards. A variety of well-documented procedures are known to transform the carbon–sulfur bond into the carbon–hydrogen bond or the carbon–carbon bond. Review articles concerning the extrusion of a sulfur moiety[5] and the selective dealkylations of sulfides[6] have recently appeared in the literature. The reduction of the carbon–sulfur bonds by alkali metals and organoalkali metal compounds[7] and by trialkyltin hydride reagents[8] has briefly been reviewed.

Several transition metal compounds are particularly thiophilic. Heterogeneous hydrodesulfurization of organosulfur compounds with Raney nickel has been one of the most important methods to reduce organosulfur compounds.[9,10] Studies on the homogeneous model for the heterogeneous hydrodesulfurization process have been enormous.[11] During the past decade significant advances have taken place in the transition metal-mediated cleavage of the carbon–sulfur bond. This review concentrates on the synthetic applications of the latter reaction. Only the transformation of carbon–sulfur bonds into carbon–hydrogen and into carbon–carbon bonds under homogeneous conditions will be considered. The literature coverage includes 1988 and some early 1989 papers.

2. Reduction of C–S Bonds with Metal Carbonyls

The interaction of organosulfur compounds with iron carbonyl was discovered in 1960 when thiophene was treated with triiron dodecacarbonyl [$Fe_3(CO)_{12}$] to give an orange-colored sulfur-containing organoiron complex.[12] This observation demonstrates the first example of the cleavage of the carbon–sulfur bond by means of a transition metal complex under homogeneous conditions. Since then, numerous sulfur-containing organometallic complexes have been synthesized by this method.[13] Moreover, metal carbonyl can serve as a low-valent reducing agent; hence the carbon–sulfur bond can be reductively cleaved.

2.1 Desulfurization of Thiols

Molybdenum(II) species generated *in situ* from molybdenum hexacarbonyl [$Mo(CO)_6$] in boiling acetic acid have been proved to be exceedingly useful for the conversion of thiols to hydrocarbons.[14] As shown in Table 1, benzylic, aryl as well as aliphatic thiols are reduced

Table 1. Reduction of Thiols with Metal Carbonyls

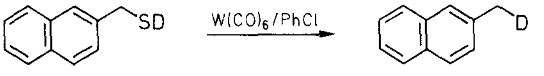
$$R{-}SH \longrightarrow R{-}H$$

R	Reagent	Solvent	Yield (%)	Ref.
Ph_3C	$Mo(CO)_6$	HOAc	76	14
	$W(CO)_6$	PhCl	78	16
1-naphthylCH_2	$Mo(CO)_6$	THF	79	15
2-naphthylCH_2	$Mo(CO)_6$	THF	67	15
4-$MeOC_6H_4$	$Mo(CO)_6$	HOAc	92	14
		THF	71	15
4-ClC_6H_4	$Mo(CO)_6$	THF	61	15
2-naphthyl	$Mo(CO)_6$	HOAc	63[a]	14
		THF	43	15
		PhCl	43[b]	16
$Me(CH_2)_{11}$	$Mo(CO)_6$	HOAc	83[a]	14
$PhO(CH_2)_8$	$W(CO)_6$	PhCl	65	16
1-adamantyl	$W(CO)_6$	PhCl	70	16

[a] RSAc is obtained as the side product.
[b] $Naph_2S$ is also isolated in 18% yield.

satisfactorily. Bridgehead thiols, for example adamantane-1-thiol, give the corresponding thioacetate and no reduction occurs.[14]

Molybdenum hexacarbonyl in boiling tetrahydrofuran is a selective desulfurization agent;[15] benzylic and aryl thiols are reduced efficiently (Table 1). Aliphatic as well as bridgehead thiols remain intact under the reaction conditions.[15] Tungsten hexacarbonyl [$W(CO)_6$] in refluxing chlorobenzene, however, provides more reactive conditions for the desulfurization of thiols (Table 1).[16] Consequently, adamantane-1-thiol is reduced to adamantane in good yield. It is noted that the tungsten-mediated reaction is carried out at higher temperature; this may account for the smooth reduction of aliphatic thiols. It has been established that $W(CO)_6$-mediated desulfurization reactions proceed via a free radical mechanism and the S–H group serves as the hydrogen source for the reaction.[16] The deuterium labelled compound can be prepared accordingly. To illustrate this, 2-naphthylmethanethiol-*d* (**1**) is treated with $W(CO)_6$ in chlorobenzene to give 2-methylnaphthalene-α-d_1 (**2**).[16]



1 **2**

In the presence of phase-transfer catalysts, benzylic thiols are desulfurized with equimolar quantities of $Fe_3(CO)_{12}$ or dicobalt octacarbonyl [$Co_2(CO)_8$] (Table 2).[17] An electron-transfer mechanism is proposed. Aliphatic and aromatic thiols fail to react under these conditions.

Table 2. Phase-Transfer Catalyzed Desulfurization of Benzylic Thiols with Metal Carbonyls[17]

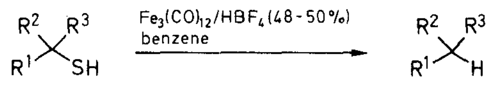
$$R^1R^2R^3C\text{-}SH \longrightarrow R^1R^2R^3C\text{-}H$$

R^1	R^2	R^3	Reagent[a]	Yield (%)
Ph	Ph	Ph	A	65
			B	82
Ph	Ph	H	A	82[b]
			B	84[b]
4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	A	80
			B	98
Ph	4-$MeOC_6H_4$	H	A	85
			B	100
4-$CH_3C_6H_4$	H	H	A	58[b]
			B	79[b]

[a] A: $Fe_3(CO)_{12}$ B: $Co_2(CO)_8$.

[b] Sulfide and disulfide are obtained as byproducts.

Under acidic and biphasic conditions (equal volumes of benzene and 48–50 % aqueous HBF_4) at room temperature, benzylic thiols are reduced by $Fe_3(CO)_{12}$ in moderate to good yields (Scheme A).[18] However, side products such as sulfides and disulfides are occasionally obtained.



R^1	R^2	R^3	Yield (%)
Ph	Ph	Ph	84
4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	H	94
2,4-$Cl_2C_6H_3$	H	H	74

Scheme A

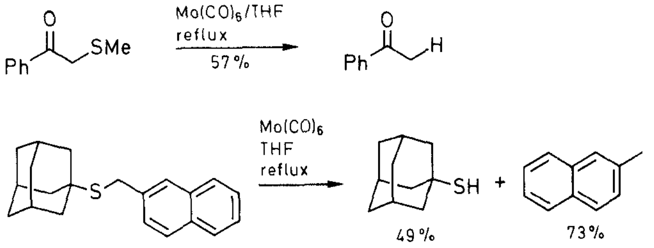
Benzylic and aromatic thiols are hydrodesulfurized upon treatment with carbon monoxide in benzene/water in the presence of a catalytic amount of $Co_2(CO)_8$ (Schemes **B**).[19] It is interesting to mention that carbonylation occurs when an alcohol is used in place of water (see Section 7).

$$RSH \xrightarrow[\text{benzene, 62 atm, 185-190°C}]{Co_2(CO)_8/CO/H_2O} RH$$

R	Yield (%)	R	Yield (%)
4-$CH_3C_6H_4CH_2$	84	2,4-$Cl_2C_6H_3CH_2$	63
4-$MeOC_6H_4CH_2$	58	3-$CH_3C_6H_4$	55
4-$ClC_6H_4CH_2$	44	4-BrC_6H_4	77
2-$CH_3C_6H_4CH_2$	48	1-naphthyl	91

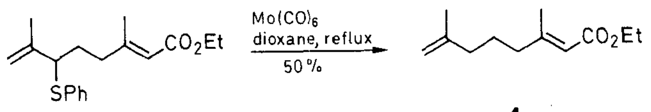
Scheme **B**

2.2 Desulfurization of Sulfides

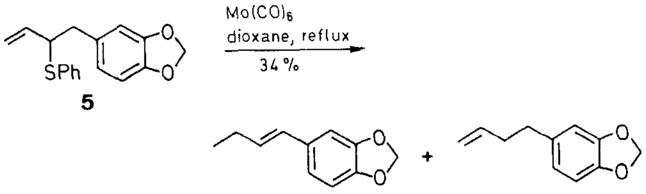


Scheme **C**

Sulfides, in general, are more difficult to desulfurize with metal carbonyls. Reactive carbon–sulfur bonds such as benzylic or those α to a carbonyl group can readily undergo reductive cleavage with $Mo(CO)_6$ in boiling tetrahydrofuran (Scheme **C**).[15] This reaction



3 **4**

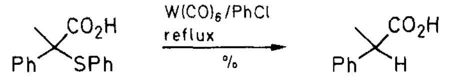


5

6 (> 95%) **7** (< 5%)

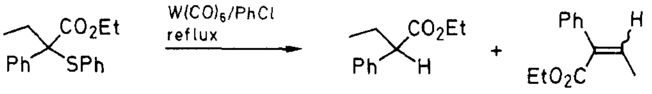
may be used to selectively cleave a benzylic carbon–sulfur bond, in the presence of an aliphatic carbon–sulfur bond, which remains intact. This procedure may provide an alternative method for the removal of the benzylic protective group, liberating the free thiol. In a similar manner, allylic sulfides are reduced with $Mo(CO)_6$ in refluxing dioxane.[20] Thus, the reduction of **3** gives **4** in 50% yield. However, the yields are not always satisfactory and double-bond migration may occur. For example, **5** affords a mixture of **6** and **7**.

Treatment of sulfides with $W(CO)_6$ in refluxing chlorobenzene generally gives the desulfurized dimer as the predominant product, if not the sole product, due to the lack of the hydrogen source (see Section 6).[16] However, when "active" hydrogen is present in the molecule, reduction does occur. Hence, sulfide **8** is treated under these conditions to give the corresponding reduced product **9**.[16]



8 **9**

Interestingly, disproportionation products have been found from the reaction of a sterically crowded sulfide.[16] Thus, treatment of **10** with $W(CO)_6$ in refluxing chlorobenzene yields a mixture of the reduced product **11** and the olefins **12**. The ratio of **11** to **12** is 1 to 1 and the *E*/*Z* isomer ratio in **12** is 4 to 1. The reaction may proceed via intermolecular hydrogen atom transfer between two radical intermediates.[16]



10 **11** 1 : 1 **12** (*E*/*Z*, 4:1)

3. Reduction of C–S Bonds with Complex Hydrides in the Presence of Transition Metal Compounds

Low-valent transition metal complexes generated *in situ* are particularly versatile in the reduction of various functional groups.[21] The activation of bivalent sulfur compounds with transition metal halides is well-documented.[22–24] It is well known that reductive fission of sulfides does not proceed with complex hydrides.[25] The reduction of carbon–sulfur bonds by the combined use of transition metal halides and complex hydride has been extensive. The results on the reduction of thiols and sulfides are tabulated in Tables 3 and 4, respectively.

As can be seen from Tables 3 and 4, copper(II) chloride ($CuCl_2$),[26,27] titanium tetrachloride ($TiCl_4$),[28] nickel(II) bromide di(triphenylphosphine) [$NiBr_2(PPh_3)_2$],[29] iron(II) chloride ($FeCl_2$),[30] $FeCl_2$ on alumina,[31] and cobalt(II) chloride ($CoCl_2$),[30] have been used for this purpose. The reducing agent can be either lithium aluminum hydride ($LiAlH_4$) or sodium triethylborohydride. Thiols are reduced successfully with complex hydride in the presence of nickel, iron or cobalt halide. The yields appear to be independent on the nature of the carbon–sulfur bonds. In other words, benzylic, aromatic, aliphatic and even bridgehead thiols are reduced smoothly. Vanadium(III) chloride (VCl_3) seems to be less reactive for the reduction of arenethiols.[30]

Sulfides are also reduced conveniently. Among the conditions shown in Table 4, $CuCl_2$ is only active toward benzylic or allylic sulfides. Titanium and nickel reagents

Table 3. Reduction of Thiols with Complex Metal Hydrides and Transition Metal Halides

$$R{-}SH \longrightarrow R{-}H$$

R	Reagent[a]	Yield (%)	Ref.
2-naphthyl CH_2	A	80	29
$4\text{-}MeOC_6H_4$	B	63	30
Ph_3C	B	59	30
2-naphthyl	A	50	29
	B	81	30
	C	39	31
	D	72[b]	30
2-fluorenyl	A	83	29
1-adamantyl	A	52	29
	C	73	31
$CH_3(CH_2)_{11}$	B	78	30
$CH_3(CH_2)_9$	A	60	29

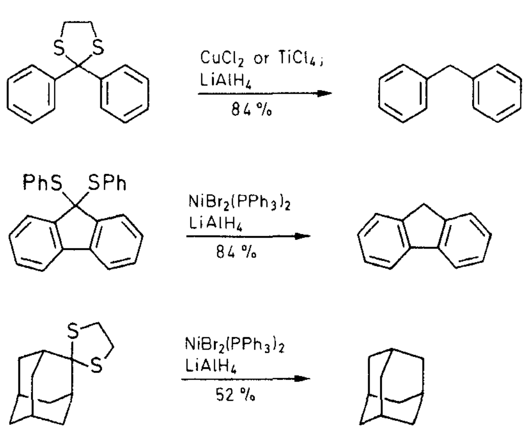
[a] A: $NiBr_2(PPh_3)_2/LiAlH_4$; B: $FeCl_2/NaEt_3BH$; C: $FeCl_2/Al_2O_3/NaEt_3BH$; D: $CoCl_2/NaEt_3BH$.
[b] Binaphthyl is obtained in 27% yield.

Table 4. Reduction of Sulfides with Lithium Aluminum Hydride and Transition Metal Halides

Substrate	Metal Halide	Product	Yield (%)	Ref.
Ph_2CHSPh	$CuCl_2$	Ph_2CH_2	94	26, 27
$4\text{-}MeOC_6H_4CH(SEt)Ph$	$CuCl_2$	$4\text{-}MeOC_6H_4CH_2Ph$	73	26, 27
$(2\text{-naphthylCH}_2)_2S$	$NiBr_2(PPh_3)_2$	2-naphthylCH_3	72	29
2-naphthylCH_2SPh	$NiBr_2(PPh_3)_2$	2-naphthylCH_3	64	29
2-naphthylSCH_3	$NiBr_2(PPh_3)_2$	naphthyl-H	53	29
1-naphthylSPh	$TiCl_4$	naphthyl-H	56	28
$Ph(CH_2)_2(SEt)C{=}CHCH_2Ph$	$TiCl_4$	$Ph(CH_2)_5Ph$[a]	80	28
2-naphthylCH_2S-(1-adamantyl)	$NiBr_2(PPh_3)_2$	adamantyl-H	45	29
		2-naphthylCH_3	70	
$(PhCH_2CH_2)_2CHSEt$	$TiCl_4$	$Ph(CH_2)_5Ph$	83	28

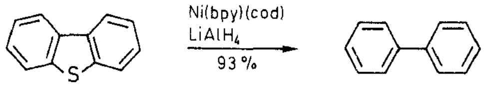
[a] $Ph(CH_2)_2CH{=}CHCH_2Ph$ is also isolated in 5% yield.

are more versatile. When diaryl ketone dithioacetals are allowed to react with $LiAlH_4$ in the presence of $CuCl_2$,[26,27] $TiCl_4$,[28] or $NiBr_2(PPh_3)_2$,[29] the corresponding reduced products are obtained in good yields (Scheme **D**).



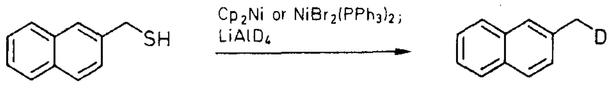
Scheme **D**

Both nickel(0)[32,33] and nickel(II)[34,35] organometallic compounds are equally well in the hydrodesulfurization reactions. (Bipyridyl)(cyclooctadiene)nickel(0)/lithium aluminum hydride is very effective for the hydrodesulfurization of dibenzothiophene (**13**) to give biphenyl (**14**);[32,33] an electron-transfer mechanism has been proposed. The nickel compound alone is desulfurization agent for **13**,[32,36] however, the yields are improved significantly in the presence of lithium aluminum hydride.[32]



13 **14**

The di(cyclopentadiene)nickel(0) (nickelocene)/lithium aluminum hydride system has been studied in detail.[34,35] The results are outlined in Table 5. Isolated double-bond and carbonyl functions can survive under the reaction conditions, however, side reactions have been observed in certain functional groups. For example, a nitro group is reduced to an amino group with this reagent.[34,35] Conjugated enones are converted to saturated ketones.[35] When lithium aluminum deuteride ($LiAlD_4$) is employed, benzylic thiol **1** gives the deuterated product **2**.



1 **2**

It is interesting to note that this nickelocene reagent also serves as a homogeneous catalyst for hydrogenation.[37] This behavior is very similar to that of Raney nickel and it is believed that such systems can serve as a homogeneous model for the reactions catalyzed by Raney nickel.[34,35]

Palladium tetra(triphenylphosphine) $[Pd(PPh_3)_4]/LiBHEt_3$ has been shown to reduce allylic sulfides,[38] however, isomerization of double bond occurs under these conditions.

The use of transition metal compounds and complex hydrides under homogeneous conditions in the desulfurization of sulfoxides and sulfones has little been explored. Nickel[29,35] and palladium[38] complexes are the only known reagents for the removal of the sulfur moiety. The results are tabulated in Table 6. As sulfoxides and sulfones can readily be reduced to sulfides by low-valent transition metal complexes or by complex hydrides,[39] it has been suggested that nickel reagents first reduce sulfoxides or sulfones to the corresponding sulfides which are further reduced under the reaction conditions. Indeed, sulfides are isolated from the reactions of the corresponding sulfoxides or sulfones as side products when insufficient reducing agent is used.[35] As a result, an excess amount of the reducing agent is usually required to effectively reduce these substrates.

Nickel boride generated *in situ* from the mixture of nickel chloride and excess sodium borohydride is a well-known

Table 5. Reduction of Thiols and Sulfides with Nickelocene/$LiAlH_4$[34,35]

$$R^1-S-R^2 \longrightarrow R^1-H$$

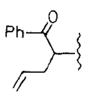
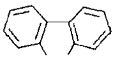
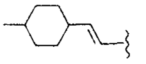
R^1	R^2	Yield (%)
1-naphthylCH_2	H	83
2-naphthyl	H	74
$CH_3(CH_2)_9$	H	41
1-adamantyl	H	46
$MeO_2CC_6H_4CH_2$	H	40
2-naphthylCH_2	2-naphthylCH_2	67
	CH_3	78
		70

Table 6. Reduction of Sulfoxides and Sulfones

$$R^1-SO_n-R^2 \longrightarrow R^1-H$$

R^1	R^2	n	Reagent[a]	Yield (%)	Ref.
2-naphthylCH_2	2-naphthylCH_2	1	A	47	35
			B	70	29
$CH_3(CH_2)_9$	Ph	1	B	55	29
2-fluorenyl	2-fluorenyl	1	B	70	29
2-naphthylCH_2	CH_3CH_2	2	A	54	35
			B	92	29
$PhCOCH_2$	Ph	2	A	63	35
	Ph	2	C	65	28

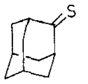
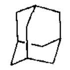
[a] A: $Cp_2Ni/LiAlH_4$; B: $NiBr_2(PPh_3)_2/LiAlH_4$; C: $Pd(PPh_3)_4/LiEt_3BH$.

desulfurization agent.[40-46] The reactions are heterogeneous and normally require large excess of the reagent. Thiols, sulfides, disulfides, dithioacetals as well as sulfoxides can all be hydrodesulfurized smoothly. Sulfones, on the other hand, remain intact under the reaction conditions.[41,45]

4. Miscellaneous Reduction Methods

Certain transition metal hydrides can undergo reductive fission of the carbon-sulfur bond. The hydridotetracarbonylferrate anion generated *in situ* has been shown to be a useful desulfurization reagent.[47] Thioketones and thioamides are transformed into the corresponding hydrocarbons and amines, respectively (Table 7). Simple allylic sulfides are reduced with rhodium hydride complexes in good to excellent yields,[48,49] however, isomerization of double bonds generally occurs. Aromatic carbon-sulfur bonds can also be reductively cleaved but longer reaction times are required. The cobalt and ruthenium hydride complexes are much less reactive in this reaction.[48]

Table 7. Reduction of Thioketones and Thioamides with $HFe(CO)_4$[47]

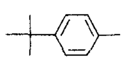
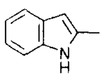
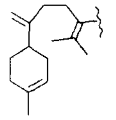
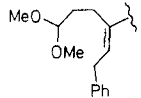
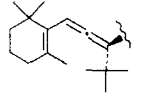
Substrate	Product	Yield (%)
$Ph_2C{=}S$	Ph_2CH_2	60
$(4\text{-}CH_3C_6H_4)_2C{=}S$	$(4\text{-}CH_3C_6H_4)_2CH_2$	61
$(4\text{-}MeOC_6H_4)_2C{=}S$	$(4\text{-}MeOC_6H_4)_2CH_2$	77
$(4\text{-}Me_2NC_6H_4)_2C{=}S$	$(4\text{-}Me_2NC_6H_4)_2CH_2$	81
		74
PhCSNHPh	$PhCH_2NHPh$	38
MeCSNHPh	EtNHPh	51

Secondary Grignard reagents in the presence of the nickel or iron catalyst are active for the reductive cleavage of the carbon-sulfur bonds. The former combination serves as an *in situ* source of "NiH" which is believed to be responsible for the reduction.[50]

Thiols, sulfides and sulfones can be reduced with ease under these conditions;[51-59] the results are collected in Table 8. The reduction is stereospecific with no over reduction being detected.[50] Acetals, ethers, aromatic systems, isolated olefins appear to be compatible with these reaction conditions. However, the reaction seems to be very much ligand dependent. To illustrate this, when triphenylphosphine is used as the ligand, reduction occurs as shown in Table 8. On the other hand, when bidendate ligands are employed, the coupling reaction proceeds smoothly. This latter reaction will be described in Section 5. It seems likely that the number of valence electrons in the intermediate of this catalytic reaction may play a key role in the chemoselectivity.

Table 8. Reduction of Organosulfur Compounds with Secondary Grignard Reagents in the Presence of $NiCl_2(PPh_3)_2$

$$R{-}Y \xrightarrow{NiCl_2(PPh_3)_2/R'MgX} R{-}H$$

R	Y	R'MgX	Yield (%)	Ref.
	SMe	*i*-PrMgBr	70	52
	SMe	*c*-$C_6H_{11}MgBr$	74	52
	SH	*c*-$C_6H_{11}MgBr$	70	52
	SOMe	*c*-$C_6H_{11}MgBr$	75	52
	SO_2Me	*c*-$C_6H_{11}MgBr$	73	52
	SMe	*i*-PrMgBr	50	51
	SPh	*i*-PrMgI	34	53
	SPh	*i*-PrMgBr	76	54
	SOPh	*i*-PrMgBr	41[a]	55

[a] $Ni(acac)_2$ is used as the catalyst.

5. Coupling Reactions with Organometallic Nucleophiles

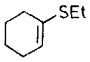
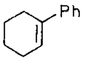
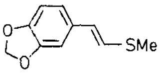
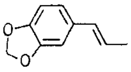
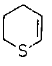
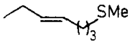
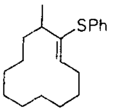
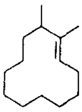
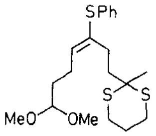
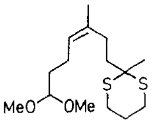
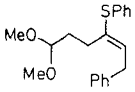
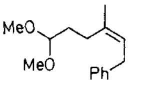
Transition metal catalyzed coupling reactions of R-X with organometallic nucleophiles are well documented,[60] R can be aryl, vinyl as well as allyl groups, and X can be any leaving groups ranging from the more reactive triflates, halides to less labile alkylthiolates, sulfones, alkoxides and even amido groups.[61] These reactions provide extremely versatile entries for the carbon-carbon bond formation.

5.1 Sulfides

Takei[62] and Wenkert[63] and their co-workers were the first to use organosulfur compounds as the substrates in such coupling reactions. Vinyl as well as aromatic sulfides are particularly useful in this transformation. A variety of olefinic and aromatic compounds have been synthesized.

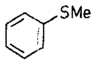
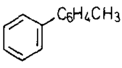
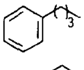
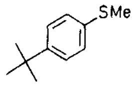
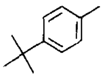
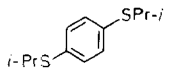
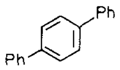
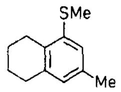
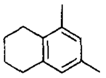
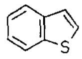
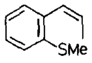
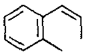
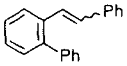
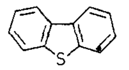
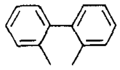
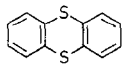
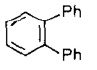
As can be seen from Tables 9 and 10, alkyl, aryl as well as allylic magnesium halides can be used in these coupling reactions. The yields are in general satisfactory. The reaction can be carried out in most of the solvents normally used for the preparation of Grignard reagents, aromatic hydrocarbon solvents such as benzene or toluene occasionally give better results. Nickel halide phosphine complexes are most widely used as the catalyst

Table 9. Coupling Reaction of Vinyl Sulfides with Grignard Reagents

Substrate	Grignard reagent	Catalyst[a]	Product	Yield (%)	Ref.
$H_2C{=}CHSPh$	PhMgBr	A	$H_2C{=}CHPh$	60	62
	PhMgBr	B		98[b]	64
$CH_3(CH_2)_5CH{=}CHSMe$	MeMgBr	A	$CH_3(CH_2)_5CH{=}CH(CH_3)$	71	63
(*Z*)-PhCH=CHSPh	PhMgBr	A	PhCH=CHPh (E/Z = 6/94)	97	62
(*E*)-PhCH=CHSMe	PhMgBr	A	PhCH=CHPh (E/Z = 95/5)	85	62
$Ph(CH_2)_2CH{=}CHSPh$	PhMgBr	A	$Ph(CH_2)_2CH{=}CHPh$	81	62
	MeMgBr	A		68	65
	EtMgBr[c]	B		59	66
	MeMgI	C		60	53
	MeMgBr	C		75	67
	MeMgBr	B		75	54

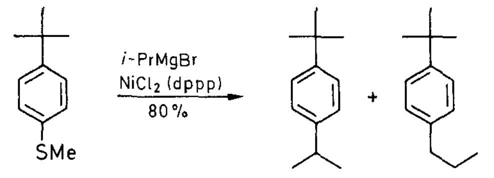
[a] A: $NiCl_2(PPh_3)_2$; B: $NiCl_2$(diphos); C: $NiCl_2$(dppp).
[b] GLC yields.
[c] Then treated with MeI.

Table 10. Coupling Reaction of Aryl Sulfides with Grignard Reagents

Substrate	Grignard reagent	Catalyst[a]	Product	Yield (%)	Ref.
	$4\text{-}CH_3C_6H_4MgBr$	A		74	63
	BuMgBr	B		96	64
	MeMgBr	A		55	63
	PhMgBr	C		84	68, 69
	MeMgBr	C		66	70
	MeMgI[b]	B		84	66
	MeMgI (excess)	B		64	66
	PhMgBr	A		61	63
	MeMgBr	A		73	63
	PhMgBr	A		80	66

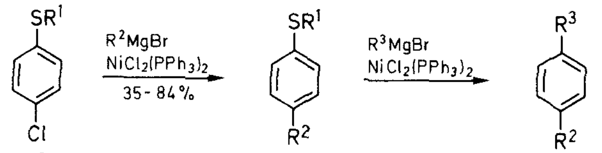
[a] A: $NiCl_2(PPh_3)_2$; B: $NiCl_2$(diphos); C: $NiCl_2$(dppp).
[b] Then treated with MeI.

in this transformation. The choice of the phosphine ligand in the catalyst sometimes is crucial in the selectivity of these reactions.[51,52,64,71–73] As mentioned in the previous section, primary or secondary Grignard reagents in the presence of $NiCl_2(PPh_3)_2$ serve as reducing agents for the reductive cleavage of thiols or sulfides. Such reaction can be suppressed simply by replacing triphenylphosphine with a bidendate ligand such as $Ph_2PCH_2CH_2PPh_2$ (diphos) and $Ph_2P(CH_2)_3PPh_2$ (dppp). It has been suggested that the bidentate ligand *could accelerate the reductive elimination step leading to* carbon–carbon bond formation. Hence, when $NiCl_2$ (dppp) is employed as the catalyst, the coupling products **16** and **17** are obtained from the reaction of **15** with *i*-PrMgBr.[52]



15 **16** **17**

The cross-coupling reactions are in general stereospecific,[68,74–80] complete retention of configuration has been observed. Different leaving groups show different reactivity in these coupling reactions, such discrepancy has been used in the chemoselective introduction of different alkyl groups. For example, the reaction of Grignard reagents with chlorophenyl alkyl sulfides **18** in the presence of $NiCl_2(PPh_3)_2$ occurs with the selective cleavage of the carbon–chlorine bond, giving the substituted phenyl alkyl sulfide **19** which can then be treated with a different Grignard reagent, yielding disubstituted-benzene **20** (Scheme **E**).[68,76]



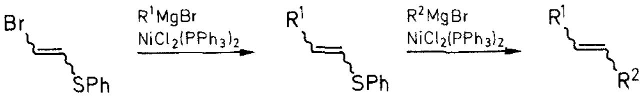
18 **19** **20**

18–20	R^1	R^2	R^3	Yield (%) of **20**
a	Me	$C(CH_3){=}CH_2$	$CH_2CH{=}CH_2$	58
b	Me	Ph	$CH_2CH{=}CH_2$	51
c	*i*-Pr	Ph	$4\text{-}CH_3C_6H_4$	65

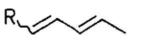
Scheme **E**

In a similar manner, the reactivity difference between halides and sulfides towards Grignard reagents in the presence of transition metal complexes has been used to selectively prepare *Z* or *E* olefins.[77] Thus, (*E*)- or (*Z*)-1-bromo-2-phenylthioethene **21** is allowed to react with the Grignard reagent in the presence of a Ni(II) or a Pd(II) catalyst to give the corresponding vinyl sulfide **22**. When an excess amount of the Grignard reagent is

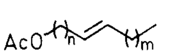
corresponding olefin **23**. Vinyl sulfide **22** can also be treated with a different Grignard reagent leading to the formation of a second carbon–carbon bond and hence, the unsymmetrical alkenes being prepared according to this scheme. (*E*)- and (*Z*)-Trimethylsilylbutadienes **24** are prepared stereospecifically.[78] The strategy of the sequential cross-coupling reaction has been effectively applied to the stereoselective syntheses of a series of mono-olefinic insect sex pheromones **25**.[79]



21 **22** **23**

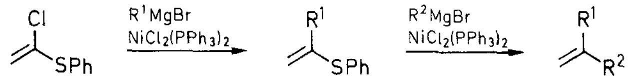


24 R = Me_3Si

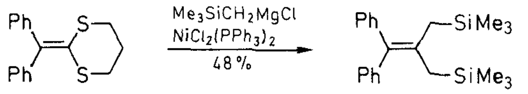


25

Similar treatment of 1-chloro-1-phenylthioethene (**26**) gives 1,1-disubstituted ethene **27**.[80] 1,1-Bis(alkylthio)alkenes can also couple with the Grignard reagents leading to the formation of two C–C bonds in one step.[52] Bis-allylsilane **29** is conveniently synthesized by using this procedure from the corresponding ketene dithioacetal **28**.[81]

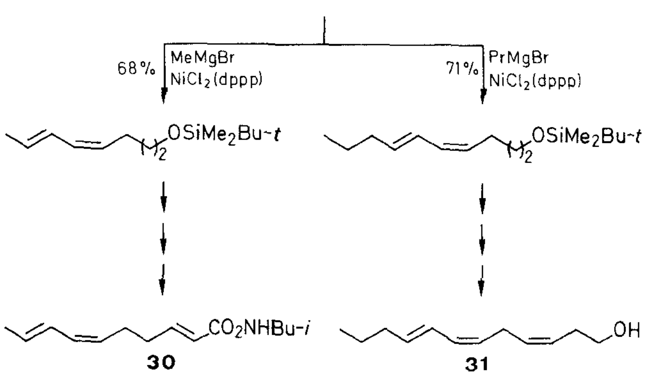


26 **27**



28 **29**

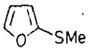
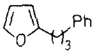
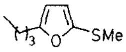
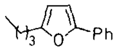
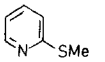
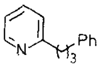
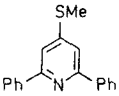
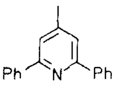
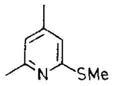
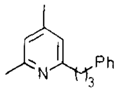
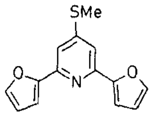
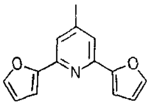
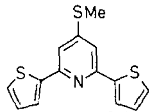
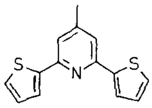
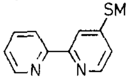
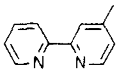
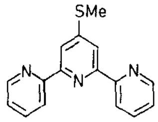
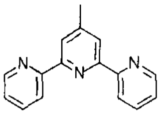
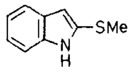
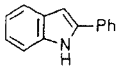
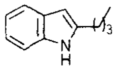
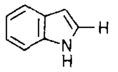
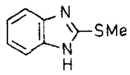
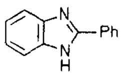
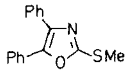
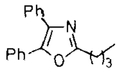
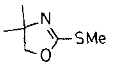
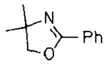
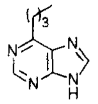
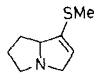
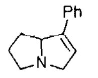
Dienyl sulfides also couple with Grignard reagents to give the corresponding alkylated dienes or trienes.[82–86] Spilanthol (**30**)[87] and a sex pheromone **31**[88] of the black carpet beetle *Attagenus megatoma* have been synthesized via this route (Scheme **F**).



30 **31**

The low-valent nickel complex catalyzed coupling reactions of sulfides with Grignard reagents have been extended to substrates containing heterocycles.[51,72,73,89-94] A variety of sulfides containing substituted pyridines,[51,72,73,89,90] bipyridines,[72] terpyridines,[73] pyrrolines,[95] pyrimidines,[89,90] benzothiazoles,[89,90] furans,[89-91] indoles,[51,72,73] purines,[94] oxazoles,[93] and oxazolines[92] have been employed for such coupling reactions (Table 11). This reaction can also be used for the modification of the purine moiety of nucleosides (Scheme G).[94]

Table 11. Coupling Reaction of Heterocyclic Aryl Sulfides with Grignard Reagents

Substrate	Grignard reagent	Catalyst[a]	Product	Yield (%)	Ref.
	Ph(CH$_2$)$_3$MgBr	C		55[b]	89, 90
	PhMgBr	B		90	91
	Ph(CH$_2$)$_3$MgBr	C		90	89, 90
	MeMgBr	A		89	51
	Ph(CH$_2$)$_3$MgBr	C		92	89, 90
	MeMgBr	A		44	51
	MeMgBr	A		26	51
	MeMgBr	A		86	72
	MeMgBr	A		80	73
	PhMgBr	C		80	51
	BuMgBr	C		58	51
				30	
	PhMgBr	C		98	89, 90
	BuMgBr	B		96	93
	PhMgBr	C D		77 84	92 92
	BuMgBr	C		74	94
	PhMgBr	A		50	95

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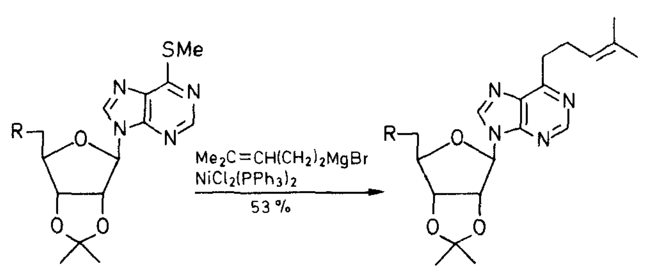
[a] A: NiCl$_2$(PPh$_3$)$_2$; B: NiCl$_2$(diphos); C: NiCl$_2$(dppp); D: PdCl$_2$(dppf).

[b] GLC yield.

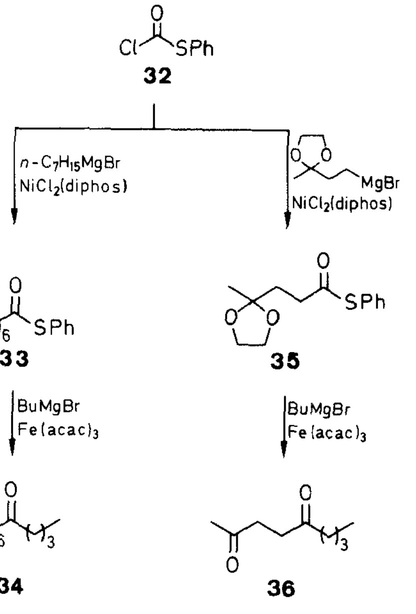


R = t-BuMe₂SiO

Scheme G

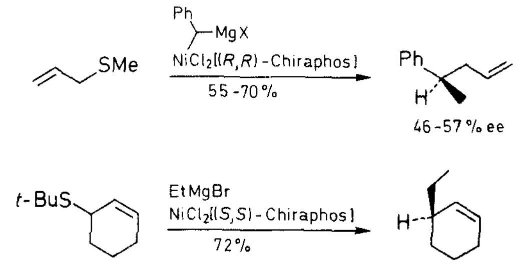
The heterocyclic rings normally remain intact under mild reaction conditions. At elevated temperature, oxazoline derivatives will further react with the Grignard reagent to give, in addition to the desired coupling product, the ring opening product in significant yield.[92] As depicted earlier (Table 10), thiophene and related compounds, *in spite of their aromatic character*, undergo desulfurization-coupling reaction to give 1,4-disubstituted dienes; the compounds exhibit retention of configuration, when appropriate.[63,66,71,96]

Palladium catalysts are in general ineffective in the catalytic cleavage of the vinylic carbon–sulfur bond.[97] As shown in Table 11, such catalysts seems to be more active than nickel catalysts in the transformation of 2-(methylthio)-2-oxazoline to alkylated 2-oxazoline.[92] The *S*-phenyl carbothioate **33** and **35** readily obtained from *S*-phenyl carbonochloridothiate **32**, can react with Grignard reagents in the presence of a catalytic amount of iron(III) acetoacetate [Fe(acac)$_3$] affording in high yields various symmetric and unsymmetric ketones **34**[98] or 1,4-diketones **36**,[99] respectively.



Simple aliphatic C_{sp^3}–S bonds are inert toward such coupling reactions under various conditions;[63] benzylic sulfides are also very unreactive. To illustrate this, benzyl methyl sulfide gives diphenylmethane in less than 9% yield upon treatment with phenylmagnesium bromide in the presence of various nickel catalysts.[97] Furthermore, 1-aryl-1-methylthioethanes remain intact under similar conditions.[100]

Allylic sulfides are more reactive under the coupling reaction conditions.[65,97,101] Nickel catalysts are most efficient, while palladium(II) or palladium(0) catalysts also promote cross coupling.[97] Since the reaction may proceed via a π-allyl intermediate, reductive elimination may occur either at α-position or at γ-position to give a mixture of regioisomers; poor regioselectivity has been observed for unsymmetrical sulfides.[97] When chiral phosphine ligands are employed, optical induction has been observed (Scheme H).[102]



Scheme H

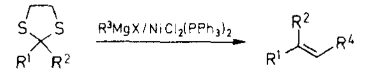
Conjugative effect may yield preferentially the more stable regioisomer.[103–105] Hence cinnamyl sulfides afford regiospecifically 1,3-diarylpropenes when reacted with arylmagnesium bromide in the presence of nickel catalysts.[65]

5.2 Dithioacetals

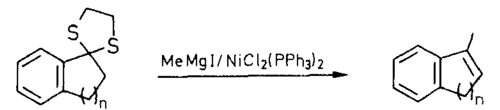
The dithioacetal group has two carbon–sulfur bonds at the same carbon atom which can, theoretically, both be replaced by nucleophiles in the cross-coupling reaction. Alternatively, an olefination reaction can also occur by a coupling process and an elimination step. Both types of the reaction have recently been discovered.[81,106–110]

The reactions of methylmagnesium iodide with benzylic dithioacetals in the presence of a catalytic amount of NiCl$_2$(PPh$_3$)$_2$ gives the corresponding olefins. As summarized in Table 12, styrenes are obtained in fairly good yields. Dithioacetals of cyclic ketones **37a,b** give exclusively endocyclic olefins **38a or b**, respectively.[106]

Table 12. Coupling of Diaryl Ketone Dithioacetals with Grignard Reagents in the Presence of NiCl$_2$(PPh$_3$)$_2$

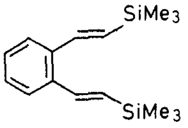


R^1	R^2	R^3	X	R^4	Yield (%)	Ref.
H	2-naphthyl	Me	I	H	94	110
H	1-naphthyl	Me	I	H	83	110
H	9-anthracenyl	Me	I	H	88	110
H	2-Me$_3$SiC$_6$H$_4$	Me	I	H	86	110
Ph	Ph	Me	I	H	70	106
		Et	Br	CH$_3$	78	106
		Bu	Br	n-C$_3$H$_7$	84	106



37a n = 1
b n = 2

38 a, b



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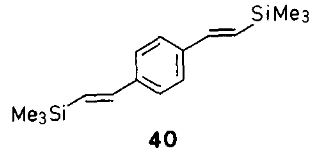
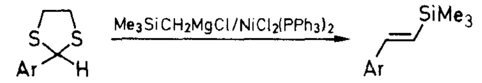


40

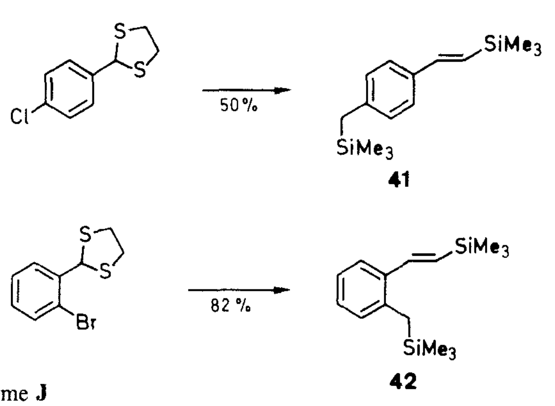
As previously discussed, benzylic sulfides generally give poor results in this coupling reaction.[97,100] The situation with diaryl ketone dithioacetals is apparently different, though the reaction may involve the benzylic sulfides as a possible intermediate;[106] presumably, the two sulfur moieties exhibit some kind of "domino effect".[100]

The reaction has been used in the stereoselective synthesis of vinylsilanes (Scheme I);[107] bis(vinylsilanes) **39** and **40** are synthesized in good yields.[107] Aryl halides also react under the reaction conditions.[60] Accordingly this reaction has been exploited in synthesizing compounds containing both a vinylic and a benzylic silyl group in one step.[107] For examples, **41** and **42** are synthesized by this procedure (Scheme J). Palladium catalysts cannot mediate coupling reactions with dithioacetals but promote reactions with aryl halides.[100] Consequently, different substituents can be introduced selectively when halobenzaldehyde dithioacetals are employed.[100]



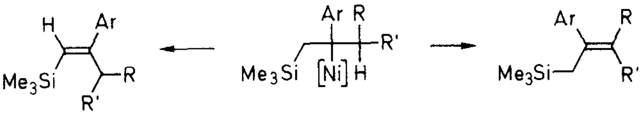
Ar	Yield (%)		
Ph	76	4-MeOC$_6$H$_4$	73
2-CH$_3$C$_6$H$_4$	71	3,4-(OCH$_2$O)C$_6$H$_3$	76
3,5-(CH$_3$)$_2$C$_6$H$_4$	71		

Scheme I

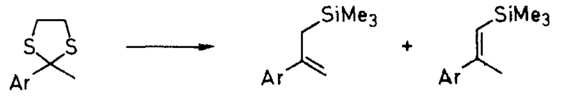


Scheme J

The reaction behavior of dithioacetals, derived from aryl alkyl ketones, with trimethylsilylmethylmagnesium chloride is of interest. These substrates contain α-hydrogen(s) and elimination of the organonickel intermediate can occur in two different orientations to give allylsilanes and/or vinylsilanes.[81]



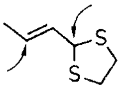
The regioselectivity of this reaction has been found to depend on the stereoelectronic effect of the substrate and of the reactive intermediate during the course of the reaction.[81,100] From dithiolanes derived from cyclic ketones, allylsilanes are obtained exclusively. From dithiolanes derived from acyclic ketones without serious steric congestion, allylsilanes are formed predominantly (Scheme K).



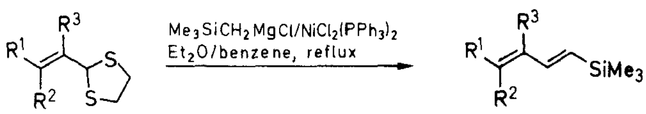
Ar	Yield (%)	Ratio **44**/**45**
Ph	82	85 : 15
2-thiovenyl	72	90 : 10
4-PhC$_6$H$_4$	81	89 : 11
1-naphthyl	69	62 : 38

Scheme K

Allylic dithioacetal **46** has two possible sites for coupling, reactions with allylic acetates and geminal diacetate are generally nonselective.[111–113] However, the sulfur moiety in **46** might have directing effect and stabilize the intermediate such that the regiochemistry of the coupling reaction could be controlled. Thus 1-trimethylsilylbutadienes and trienes are synthesized regio- and stereoselectively in good to excellent yields.[108] Some of these results are outlined in Scheme L.



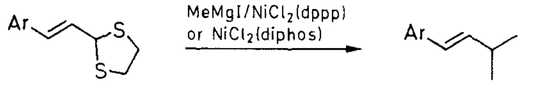
46



R^1	R^2	R^3	Yield (%)
Ph	H	H	91
Ph	H	CH$_3$	80
2-MeOC$_6$H$_4$	H	H	79
1-naphthyl	H	H	91
PhCH=CH (*E*)	H	H	88
(CH$_3$)$_2$C=C(CH$_2$)$_2$	CH$_3$	CH$_3$	93
Ph	CH$_3$	H	88

Scheme L

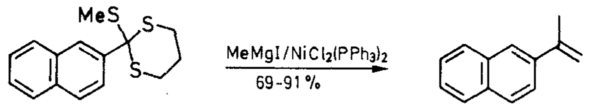
Like other transition metal catalyzed reactions, the reaction is very sensitive to the steric environment of the substrates and of the reactive intermediates. When methylmagnesium iodide is employed, the cross-coupling reactions of allylic dithioacetals lead primarily to geminal dimethylation products, in addition to a small amount of butadienes.[109] The formation of butadienes can be suppressed when bidendate ligands such as diphos or dppp are used in place of triphenylphosphine in the catalyst. As shown in Scheme **M**, the geminal dimethyl products are obtained predominantly, if not exclusively, in excellent yields. The yield of butadiene increases as the substituent at the C-2 position changes from hydrogen to methyl to ethyl. Conjugative preference is essential in these substrates.[109] This dimethylation reaction, however, provides a unique method for the conversion of an α,β-unsaturated carbonyl equivalent into the corresponding geminal dimethyl group.



Ar	Yield (%)	Ar	Yield (%)
Ph	93	3-$MeOC_6H_4$	95
4-$CH_3C_6H_4$	98	2-naphthyl	95

Scheme **M**

Preliminary experiments on the extension of this cross coupling reaction to orthothioesters were successful, for example, treatment of the benzylic orthothioester **47** with an excess amount of methylmagnesium iodide introduces the corresponding isopropenyl group to give **48** in good yield.[114]



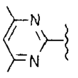
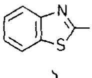
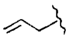
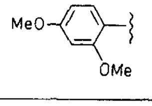
47 **48**

5.3 Thiols

Thiols[63,65,89,90] are also capable of undergoing nickel catalyzed coupling reactions with Grignard reagents (Table 13). Aromatic and allylic thiols give the desired products in good yields.

Table 13. Coupling Reaction of Thiols with Grignard reagents

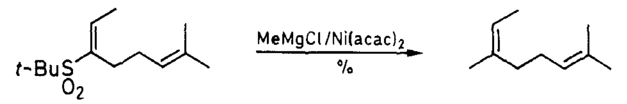
$$R^1{-}SH \xrightarrow{R^2MgBr} R^1{-}R^2$$

R^1	R^2	Catalyst[a]	Yield (%)	Ref.
Ph	4-$CH_3C_6H_4$	A	62	63
2-pyridyl	$Ph(CH_2)_3$	B	94	89, 90
	Ph	B	43	89, 90
	Bu	B	89	89, 90
		A	86	65

[a] A = $NiCl_2(PPh_3)_2$; B = $NiCl_2(diphos)$.

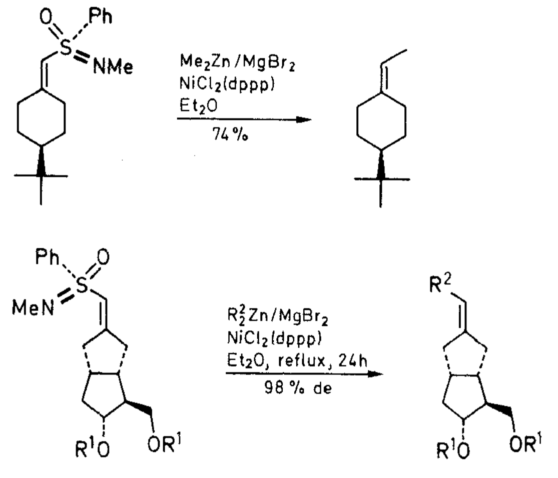
5.4 Sulfoxides, Sulfones and Related Reactions

The carbon–sulfur bond of a sulfone is relatively more reactive than that of the corresponding sulfide in the transition-metal-mediated reaction, presumably due to the better leaving ability of a sulfonyl group. Upon treatment with Grignard reagents under similar conditions as those described for sulfides, vinyl sulfones are converted to alkylated olefins. Nickel, palladium, iron as well as copper compounds can be used as catalysts.[63,115–117] The reaction in general shows high stereoselectivity. When the sulfone **49** is reacted with methylmagnesium chloride in the presence of nickel(II) acetoacetate [$Ni(acac)_2$], the olefin **50** is obtained.



49 **50**

Vinylic sulfoximines can also undergo desulfurization-coupling reaction with Grignard reagents to give in high diastereoselectivity the corresponding alkylated products (Scheme **N**).[118]



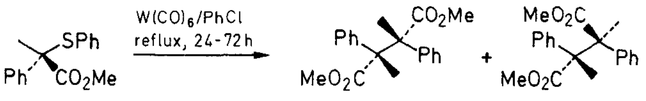
R^1	R^2	Yield (%)
$SiMe_2Bu$-*t*	Ph	83
$SiMe_2Bu$-*t*	$(CH_2)_4OSiPh_2Bu$-*t*	70

Scheme **N**

Allylic sulfones can also undergo nucleophilic substitution in the presence of transition metal catalysts. An excellent review article on this topic has recently appeared.[119] It is noteworthy that soft nucleophiles can be used in these coupling reactions. In the presence of $Mo(CO)_6$, allylic sulfides also react with soft nucleophiles in refluxing dioxane to give the corresponding coupling products.[20]

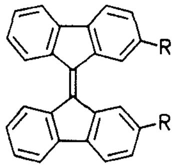
6. Desulfurdimerization Reactions

As mentioned in Section 2, thiols can be reduced with $W(CO)_6$ in refluxing chlorobenzene, the SH group serves as the hydrogen source.[16] In these reactions, dimeric products are also isolated in small amounts. Sulfides do not have such "active" hydrogen; consequently, treatment of a chlorobenzene solution of benzylic sulfide with $W(CO)_6$ affords the corresponding dimeric product in moderate yield.[16] Functional groups such as halogens, ethereal linkages as well as esters remain intact under the reaction conditions. It is particularly noteworthy that chiral sulfide **51** yields a mixture of dimeric diastereoisomers **52a,b** which do not show any optical rotation.[16]

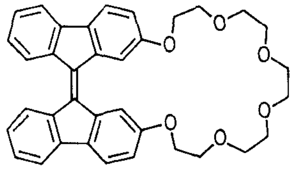


51 **52a** **52b**

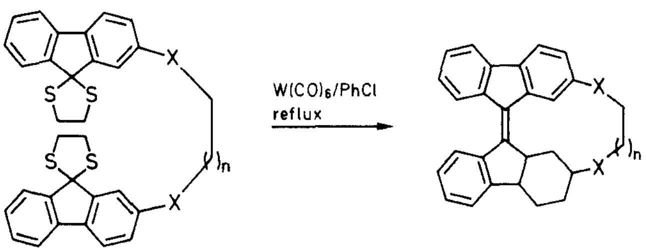
Dithioacetals can also undergo desulfurdimerization reactions under similar conditions to give in good to excellent yields the dimeric olefins,[120-124] some useful examples are outlined in Table 14. The reaction can also be carried out intramolecularly (Scheme **O**). (*Z*)-2,2'-Disubstituted bifluorenylidenes **53**[122,124] and bifluorenylidene-hinged crown ethers **54**[123] are synthesized in good yields. The first chiral bifluorenylidenes were synthesized by intramolecular desulfurdimerization of two fluorenone dithioacetal moieties linked with a chiral bridge (Scheme **P**).[124]



53 R = CO_2Me, CH_2OH

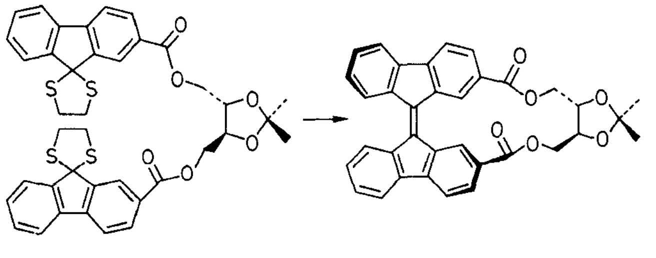


54



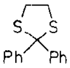
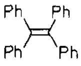
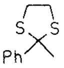
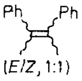
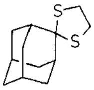
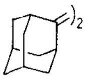
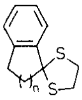
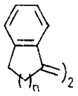
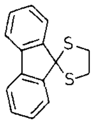
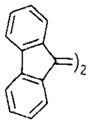
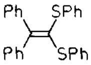
X	n	Yield (%)	X	n	Yield (%)
CO_2	1	56	O	1	37
	2	63		2	66
	3	49		3	62
				6	56
				10	58

Scheme **O**



Scheme **P**

Table 14. $W(CO)_6$-Mediated Desulfurdimerization of Dithioacetals[121]

Dithioacetal	Product	Yield (%)
		97
		59
		71[a]
		62[a] (n = 1) 61[a] (n = 2)
		93
		75

[a] *E* isomer only.

Thiobenzophenones undergo desulfurdimerization with stoichiometric dimanganese decarbonyl in heptane to afford tetraarylethylenes. Reasonable yields of olefins are also found in the reaction of the metal carbonyl with thioketones having either electron-donating or withdrawing substituents.[125] Desulfurdimerizations of thioketones can also be achieved using dicobalt octacarbonyl, the cobalt tetracarbonyl anion, or cyclopentadienyliron dicarbonyl dimer as reagents (Scheme **Q**).[126]

Ar	Reagent	Yield (%)
Ph	$Co(CO)_4^-$	45
	$Co_2(CO)_8$	71
	$[CpFe(CO)_2]_2$	55
	$Mn_2(CO)_{10}$	69
$4\text{-}CH_3C_6H_4$	$Co_2(CO)_8$	83
$4\text{-}MeOC_6H_4$	$Co_2(CO)_8$	75

Scheme **Q**

7. Carbonylation Reactions

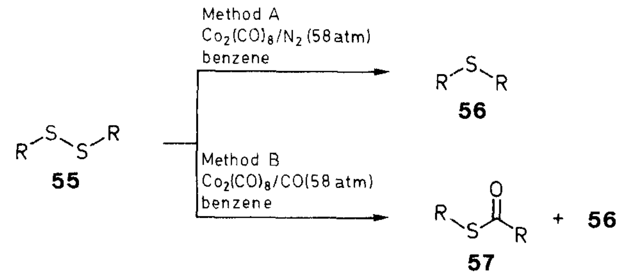
Carbonylation of organosulfur compounds has recently received much attention; $Co_2(CO)_8$ has been shown to play a unique role in this transformation. Benzylic or aromatic thiols in aqueous alcohol are treated with carbon monoxide (57–61 atm) at 190°C in the presence of a catalytic amount of $Co_2(CO)_8$ to give carboxylic esters in 25–83% yields (Scheme **R**).[127] Aryl halides are stable under the reaction conditions; in the presence of conjugated dienes, the thioester is obtained. The diene which gives the best results is 2,3-dimethoxybutadiene.[128]

$$RSH \xrightarrow{Co_2(CO)_8,\ EtOH/CO(58\text{-}61\ atm)} RCO_2Et$$

R	Yield (%)	R	Yield (%)
$4\text{-}CH_3C_6H_4CH_2$	75	2-naphthyl	50
$4\text{-}MeOC_6H_4CH_2$	68	$3\text{-}CH_3C_6H_4$	77
$4\text{-}ClC_6H_4CH_2$	67		

Scheme R

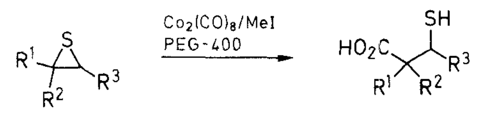
When aromtic disulfides are treated with carbon monoxide (58 atm) and a catalytic quantitiy of $Co_2(CO)_8$ in benzene, sulfides are isolated as sole products in good yields (Scheme S).[129] Benzylic disulfides, on the other hand, are nonselective; mixtures of thioesters and sulfides are usually obtained. In the presence of a radical initiator, such as di-*tert*-butyl peroxide, under similar conditions, with nitrogen used to replace the carbon monoxide, dibenzyl disulfides are desulfurized to dibenzyl sulfides in excellent yields.[129] It has been suggested that carbon monoxide retards the desulfurization reaction.



55 **56** **57** **56**

R	Conditions	Yield (%)	
		56	**57**
$PhCH_2$	A	85	
	B	53	19
$4\text{-}CH_3C_6H_4CH_2$	A	91	
	B	28	43
Ph	B		69
$3\text{-}CH_3C_6H_4$	B		82

Scheme S

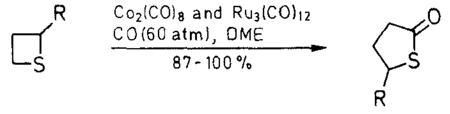


R^1	R^2	R^3	Yield (%)
H	Ph	H	78
H		$-(CH_2)_4-$	55
CH_3		$-(CH_2)_4-$	24
H		$-(CH_2)_6-$	49

Scheme T

Cobalt carbonyl catalyzes the carbonylation of thiiranes to α-mercapto acids using alkyl halides, 3 N potassium hydroxide, benzene as the organic phase, and polyethylene glycol (PEG-400) as the phase-transfer agent (Scheme T).[130]

More recently, thietanes **58** were found to undergo regiospecific carbonylation catalyzed by $Co_2(CO)_8$ and $Ru_3(CO)_{12}$ co-catalyst to give thiolactones. **59**[131] It is interesting to note that cobalt or ruthenium catalyst alone gives poorer yields.



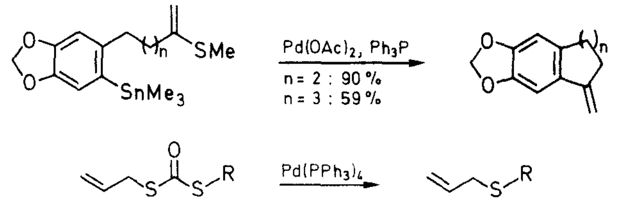
58 **59**

R = H, Me

8. Miscellaneous Reactions

The extrusion of sulfur from thiiranes to give olefins is useful in organic synthesis.[132] Several procedures using transition metal complexes have been employed as thiirane desulfurization reagents.[132] Chlorodicarbonylrhodium(I) dimer under a carbon monoxide atmosphere catalyzes the homogeneous desulfurization of thiiranes to olefins.[133] The reaction is stereospecific with rentention of configuration and is applicable to thiiranes bearing alkyl, aryl, alkoxy and ethoxycarbonyl substituents; $Co_2(CO)_8$ is inert under similar conditions.

The reaction of thioamides with iron pentacarbonyl in boiling butyl ether affords nitriles in moderate yields.[134] Reactions of sulfonyl chlorides with olefins under Heck reaction conditions yield a mixture of products where the carbon–sulfur bonds are cleaved.[135,136] Both ruthenium[136] and palladium[135] catalysts can promote these reactions. Intramolecular coupling of vinyl sulfide with an organotin moiety is promoted by palladium catalyst.[137] The reaction provides a useful entry for annulation reactions (Scheme U). Extrusion of the COS moiety from allylic dithiocarbonates **60** yields allylic sulfides **61**.[138,139]



60 **61**

Scheme U

We thank the Croucher Foundation, Hong Kong and National Science Council, ROC for support. Z.J.N. thanks the Lee Hysan Foundation for a fellowship. Thanks are also due to Professors H. Alper, M. Julia, F. Naso, H. Takei, M. Tiecco, H. Yamamoto, E. Wenkert, and Dr. L.N. Pridgen for providing us useful information.

Received: 3 May 1989

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