

## TETRAHEDRON REPORT NUMBER 94

### SYNTHETIC METHODS USING $\alpha$ -HETEROSUBSTITUTED ORGANOMETALLICS

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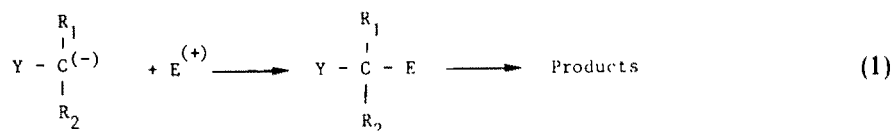
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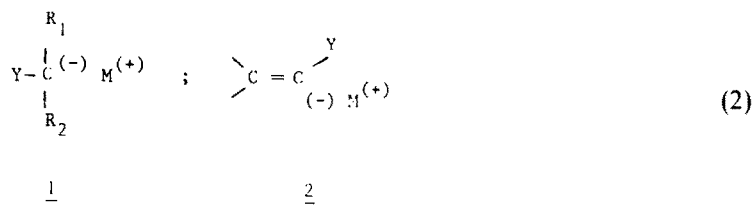
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## INTRODUCTION

$\alpha$ -Heterosubstituted carbanions<sup>1\*-39\*,53,7\*</sup> are powerful synthetic intermediates. When reacted with electrophiles they allow the formation of a new bond and permit the branching of a reactive, or a potentially reactive group, on the formed bond (Eq. 1).

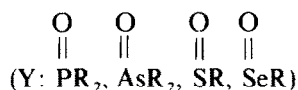


The heteroatoms (Y) generally used are N, O, Si, P, S, Cl, As, Se, Br. Among the different carbanions prepared are those in which the heteroatom is branched onto an sp<sup>3</sup> C atom (1, Eq. 2) and those which are directly branched onto an sp<sup>2</sup> carbon (2, Eq. 2).



There are other known carbanions which bear two (Y and R<sub>1</sub> heteroatoms) or three (Y, R<sub>1</sub>, R<sub>2</sub> heteroatoms) identical or different heteroatomic moieties (1, Eq. 2).

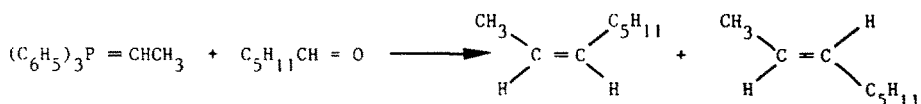
When the heteroatom belongs to either Group Va (N, P, As) or Group VIa (S, Se), different species bearing a partial or a complete positive charge on the heteroatom are known. Phosphinyl, arsinyl, sulfinyl and seleninyl,



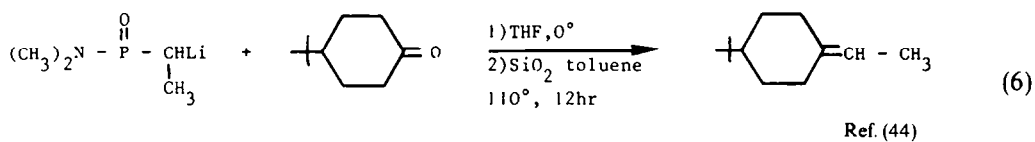
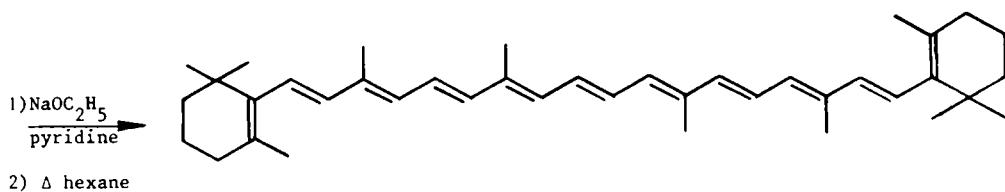
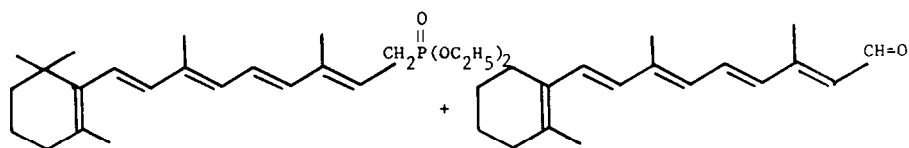
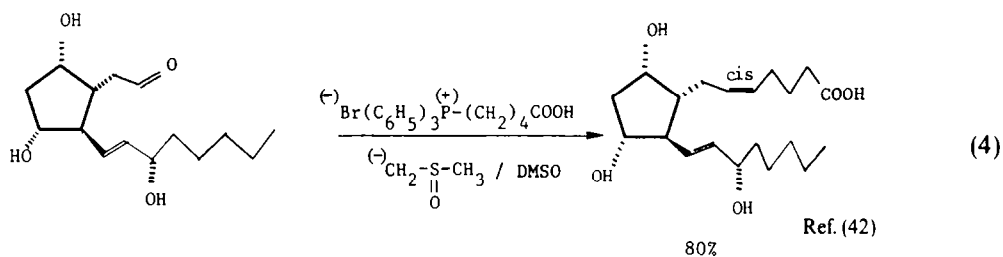
are the principal representatives of the first class, together with sulfonyl (Y = SO<sub>2</sub>-R) or nitro derivatives. Ammonium (N<sup>+</sup>R<sub>3</sub>), phosphonium (P<sup>+</sup>R<sub>3</sub>), arsonium (As<sup>+</sup>R<sub>2</sub>), sulfonium (S<sup>+</sup>R<sub>2</sub>) and selenonium (Se<sup>+</sup>R<sub>2</sub>) groups suit the second class and the corresponding carbanions (Eq. 2) are named ylides.

$\alpha$ -Heterosubstituted organometallics are implicated in several valuable synthetic transformations with concomittant new C-C bond formation. These include:

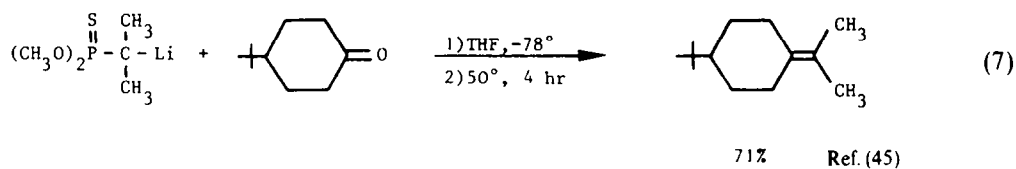
1. The synthesis of olefins from carbonyl compounds and phosphonium ylides,<sup>9\*,18\*-22\*,41,42</sup>  $\alpha$ -metallo phosphonates<sup>9\*,16\*,17\*,43</sup> and phosphonamides,<sup>44</sup> O,O'-dialkyl  $\alpha$ -lithio phosphonothioate esters,<sup>45</sup>  $\alpha$ -metallo silanes,<sup>14\*,15\*,46,47</sup>  $\alpha$ -lithiosulfides,<sup>48-52</sup>  $\alpha$ -lithiosulfoxides,<sup>53,54</sup>  $\alpha$ -lithiosulfones<sup>55,211</sup>  $\alpha$ -lithiosulfenamides,<sup>56</sup>  $\alpha$ -lithiosulfoximines<sup>69\*</sup> (Eq. 3-13) and  $\alpha$ -lithio-selenides<sup>31\*,32\*,57-61</sup> (see Chapter 11C4c).



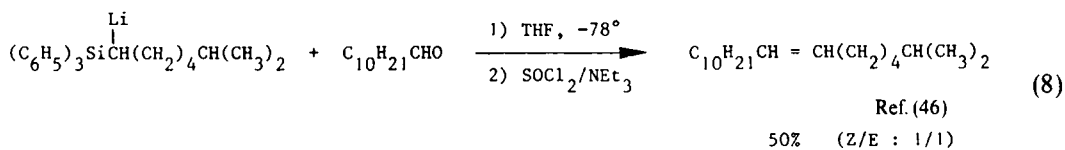
- a) 1) Salt free ylide (NaNH<sub>2</sub>/NH<sub>3</sub>)/benzene  
 2) Aldehyde 66 % overall 91% 9% Ref.(41)  
 3) tBuOK (3)
- b) 1) ylide from C<sub>6</sub>H<sub>5</sub>Li/THF  
 2) aldehyde 70 % overall 1% 99% Ref.(41)  
 3) 3 eq C<sub>6</sub>H<sub>5</sub>Li  
 4) HCl  
 5) tBuOK

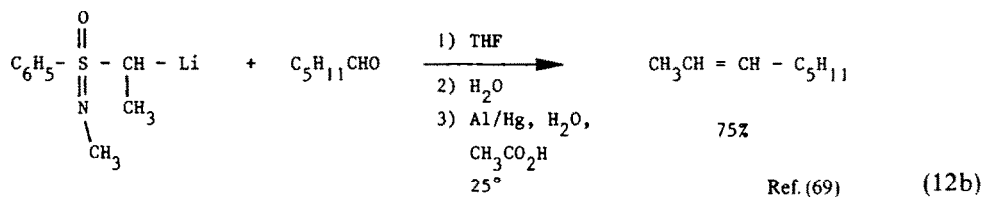
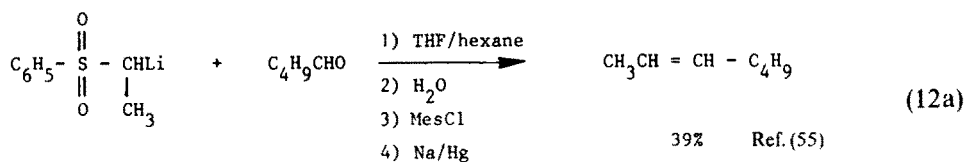
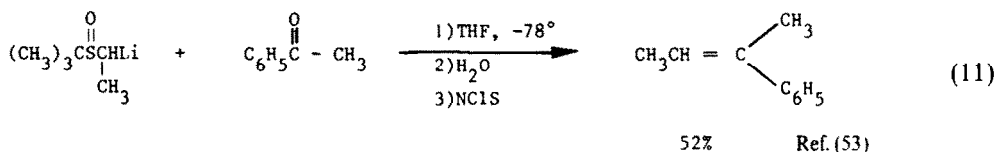
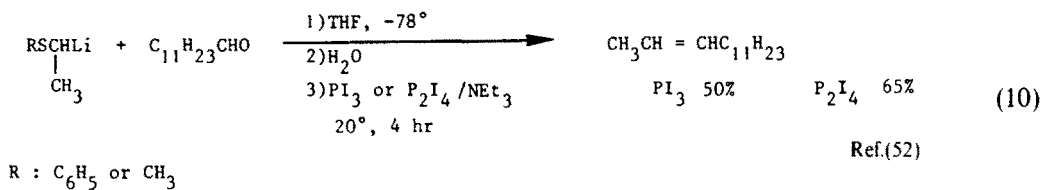
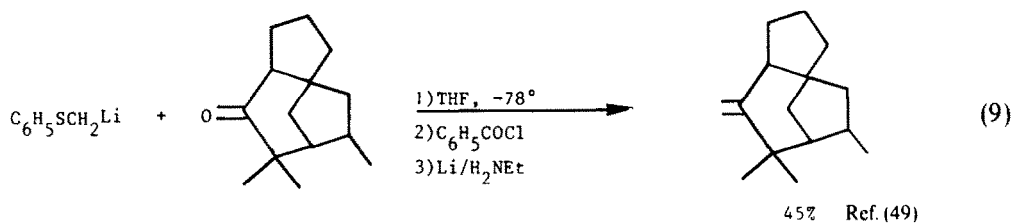


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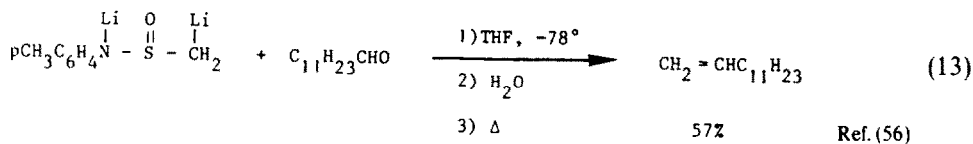


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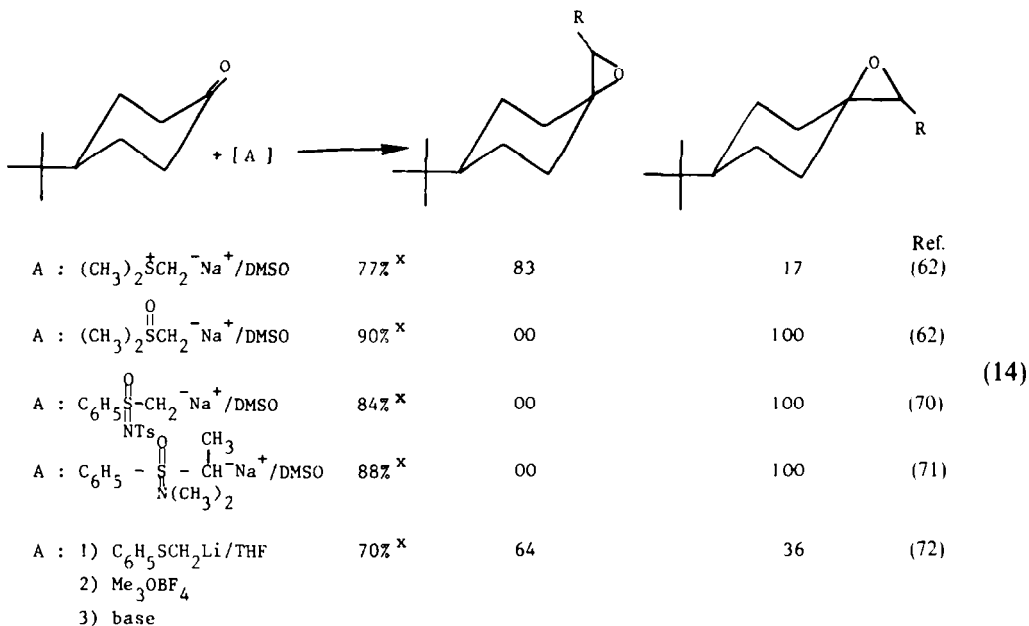


(see also ref. 404)

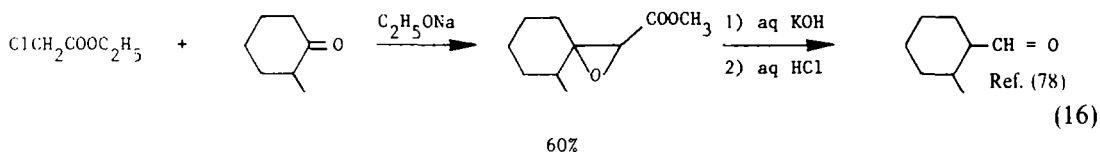
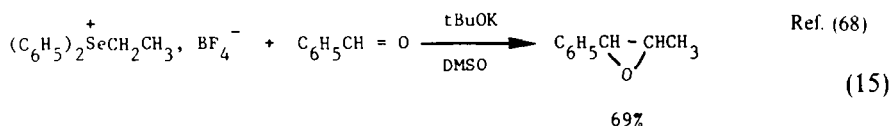


2. (a) *The synthesis of epoxides from carbonyl compounds and sulfonium ylides,<sup>9\*.23\*.28\*.62-67</sup> sulfoxonium ylides,<sup>62.66</sup> selenonium ylides,<sup>68</sup>  $\alpha$ -metallo sulfoximines,<sup>69\*-71</sup>  $\alpha$ -thioalkyllithiums,<sup>72-74</sup>  $\alpha$ -selenoalkyllithiums<sup>29\*.31\*.75-77</sup> (see Chapter III C4f) or  $\alpha$ -metallo chloroesters<sup>36\*.37\*.78</sup> and nitriles.<sup>31\*.36\*.37\*</sup> (Eqs. 14-16).*

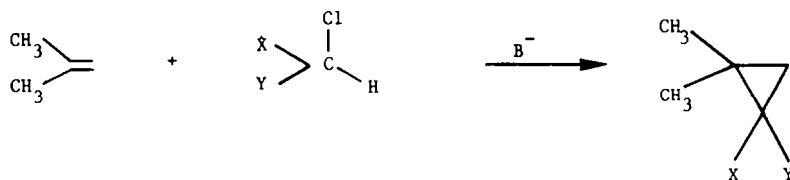
(b) *As well as the synthesis of thiiranes from carbonyl compounds<sup>79.80</sup> (Eq. 17).*



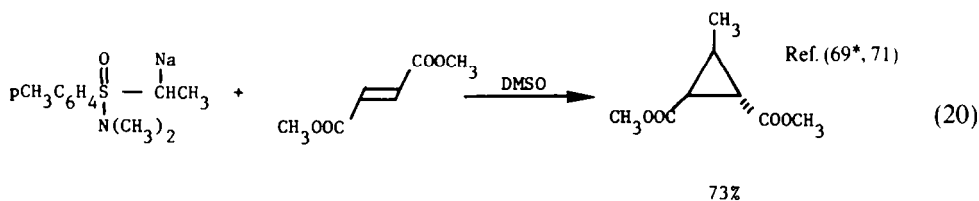
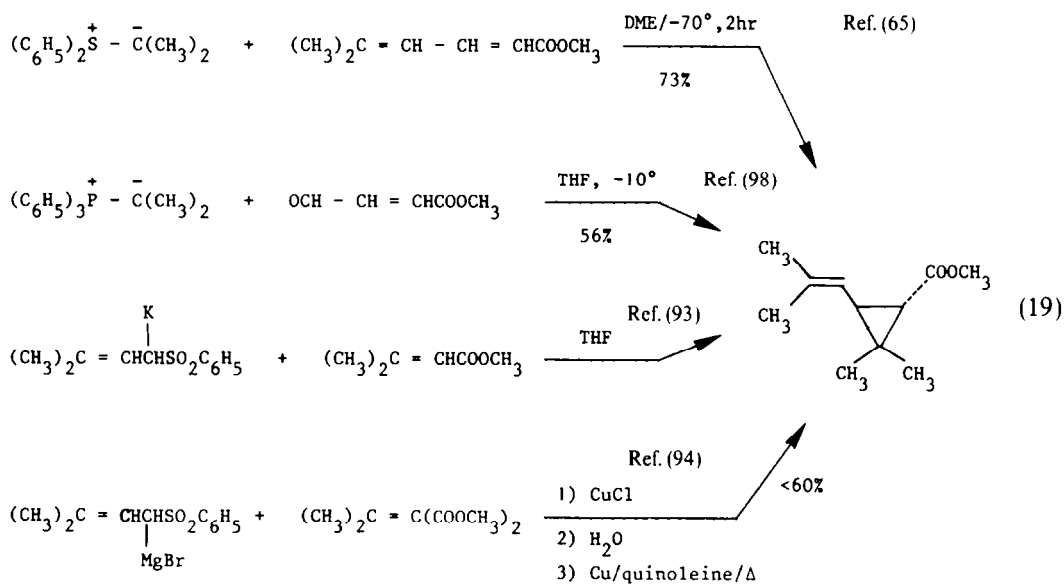
x refers to overall yield



3. *The synthesis of cyclopropanes from nucleophilic olefins and  $\alpha$ -metallo  $\alpha$ -halogenoalkanes<sup>33\*.34\*.38\*.40\*.81\*.83\*.84-90</sup> or from electrophilic olefins and nucleophilic carbenoids such as sulfur ylides,<sup>23\*.28\*.65.91-92</sup> sulfoxonium ylides,<sup>23\*.28\*.62</sup>  $\alpha$ -metallo sulfoximines,<sup>69\*.71</sup>  $\alpha$ -metallo allylsulfones,<sup>93.94</sup> phosphorus ylides<sup>21\*.95-100</sup> and  $\alpha$ -metallo nitroalkanes<sup>101.102</sup> (Eqs. 18-21).*

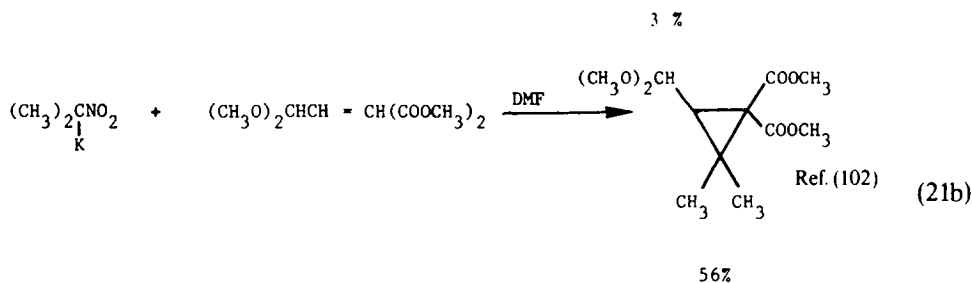


a	$\begin{array}{c} \text{Cl} \\ \diagup \\ \text{C}^{\pm} \\ \diagdown \\ \text{Cl} \end{array} \left[ \text{CHCl}_3 / \text{aq. KOH, NR}_4^+, \text{X}^- \right]$	80%	Ref. (84)
b	$\text{C}_6\text{H}_5\text{O} - \text{CH}^{\pm} \left[ \text{BuLi} \right]$ $\text{CH}_3\text{O} - \text{CH}^{\pm} \left[ \text{tBuLi} \right]$	51% 32%	(85ab) (85c)
c	$\text{C}_6\text{H}_5\text{S} - \text{CH}^{\pm} \left[ \text{BuLi} \right]$ $\left[ \text{tBuOK, } -15^\circ \right]$	60% 90%	(85e) (85c)
d	$\text{C}_6\text{H}_5\text{SeCH}^{\pm} \left[ \text{tBuOK} \right]$	70%	(86)
e	$\text{C}_6\text{H}_5\text{S} - \text{C}^{\pm} \begin{array}{c} \diagup \\ \text{Cl} \\ \diagdown \end{array}$	60%	(87a)
f	$\text{CH}_3\text{S} - \text{C}^{\pm} \begin{array}{c} \diagup \\ \text{Cl} \\ \diagdown \end{array}$	17%	(87b)



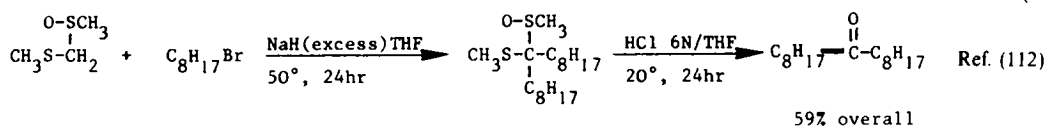
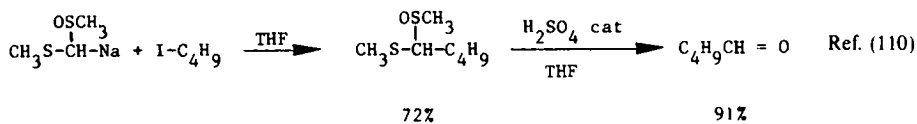
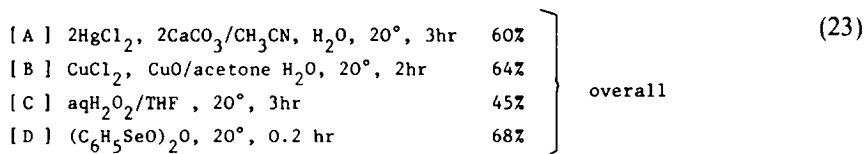
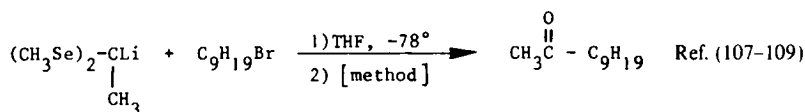
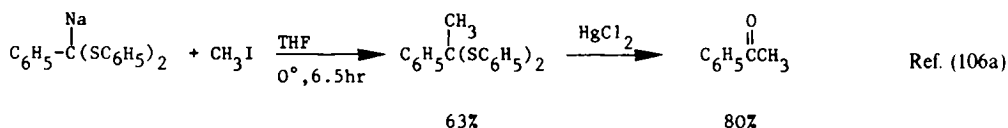
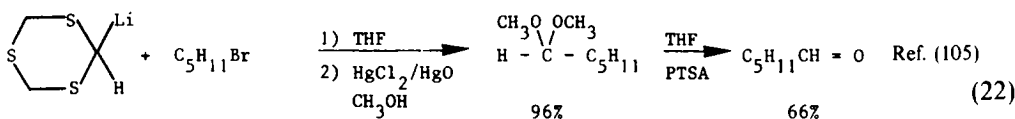
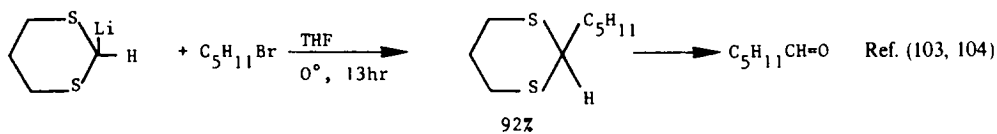


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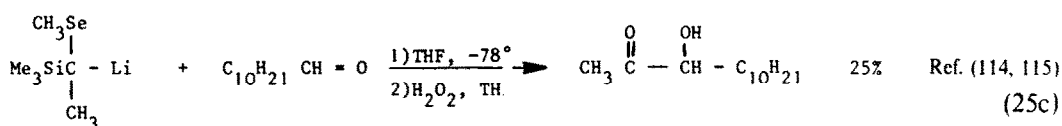
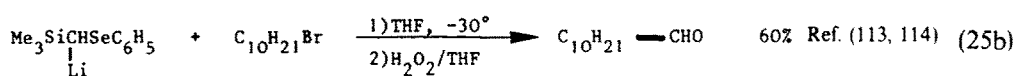
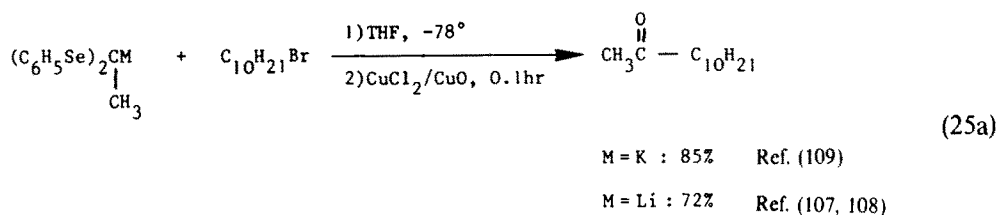


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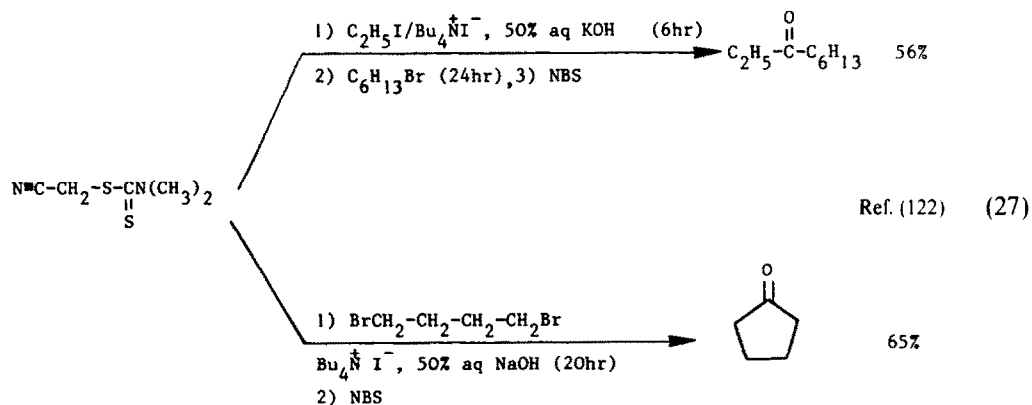
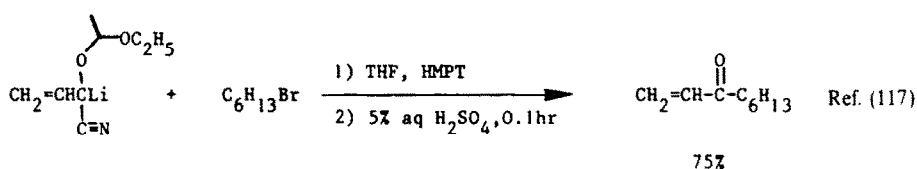
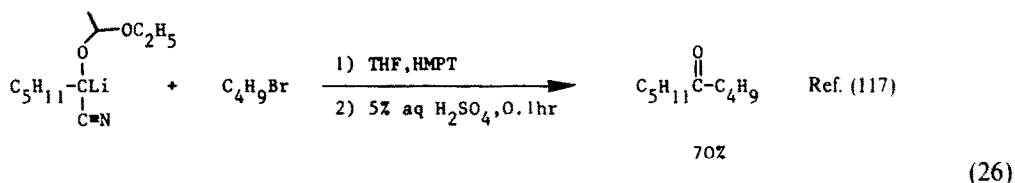
4. The synthesis of aldehydes and ketones from masked acyl anions equivalent,<sup>7\*,8\*,24\*,25\*</sup> including:  
 (a)  $\alpha$ -metallo  $\alpha$ -diheterosubstituted alkanes such as 2-lithio-1,3-dithianes<sup>103,104</sup> or -trithianes,<sup>105</sup>  $\alpha$ -lithio dithioalkanes,<sup>106</sup>  $\alpha$ -lithio diselenoalkanes,<sup>107-109</sup>  $\alpha$ -lithio S, SO dithioalkanes<sup>110-112</sup> and  $\alpha$ -lithio  $\alpha$ -silyl-selenides<sup>113-116</sup> (Eqs. 22-25).

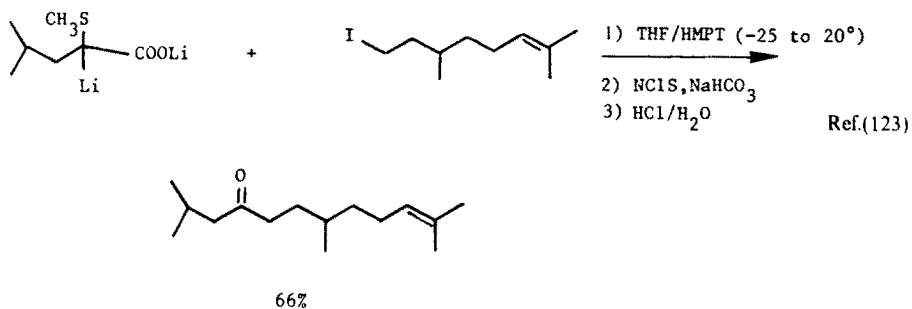




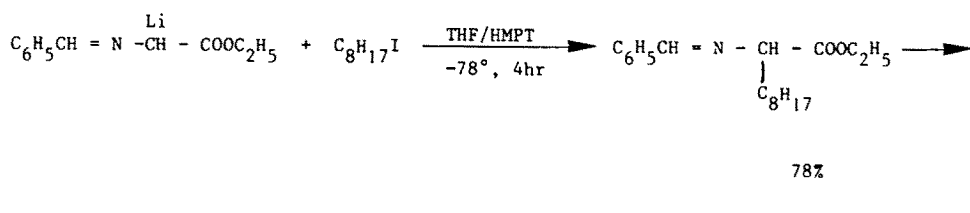


(b)  $\alpha$ -metallo monoheterosubstituted alkanes such as  $\alpha$ -lithio  $\alpha$ -alkoxynitriles,<sup>117-120, 121\*</sup> carbanions derived from  $\alpha$ -thionitriles,<sup>122</sup>  $\alpha$ -thiocarboxylic acids,<sup>123</sup> their corresponding sulfonium salts,<sup>124</sup>  $\alpha$ -lithio  $\alpha$ -imino esters<sup>125</sup> and  $\alpha$ -metallo nitroalkanes<sup>139a\*, b, c\*</sup> (Eqs. 26-29).

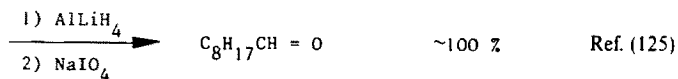




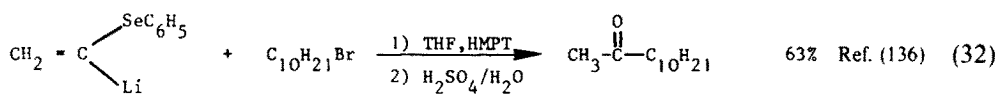
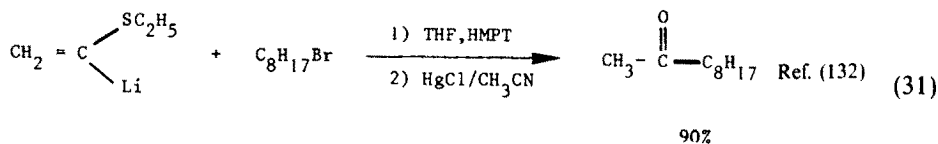
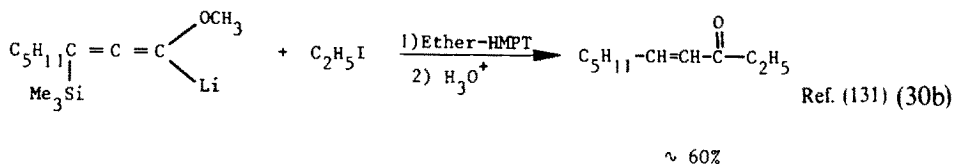
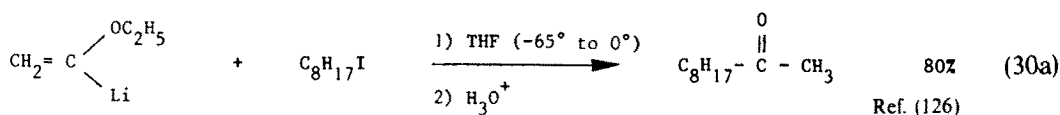
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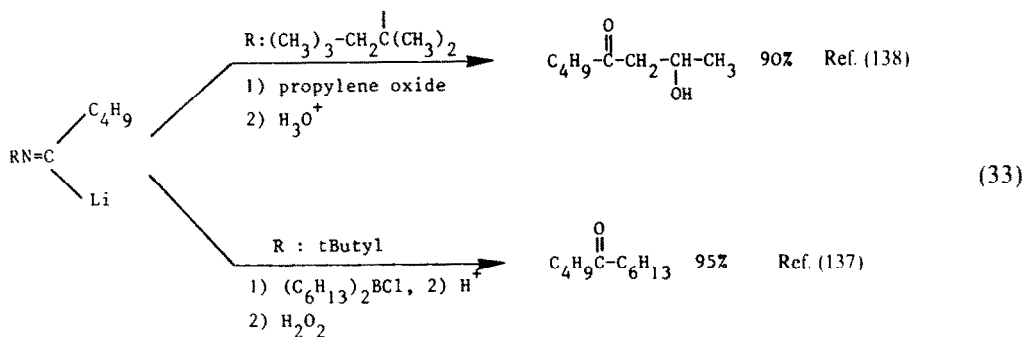


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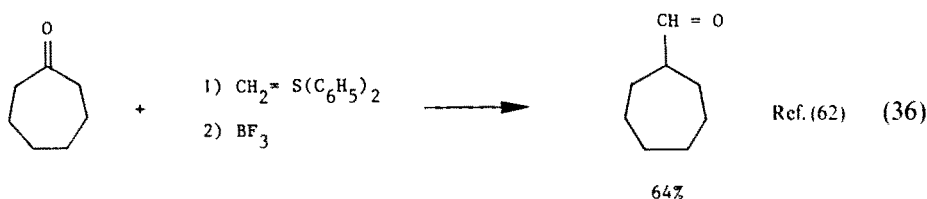
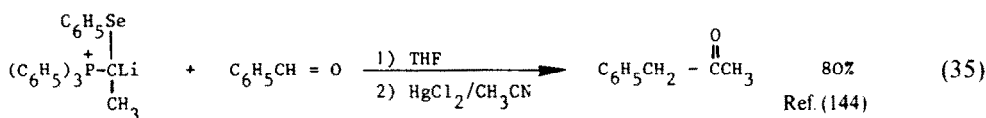
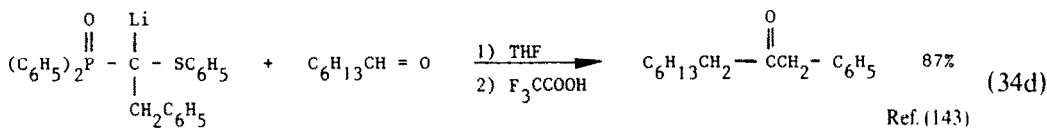
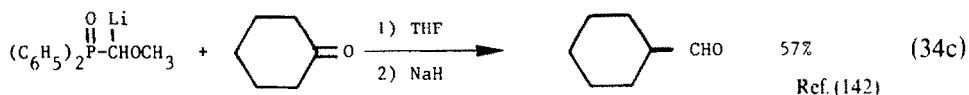
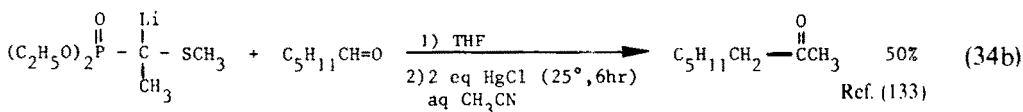
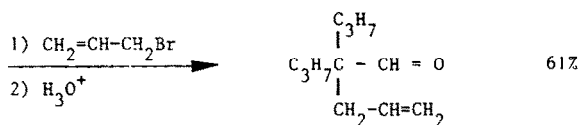
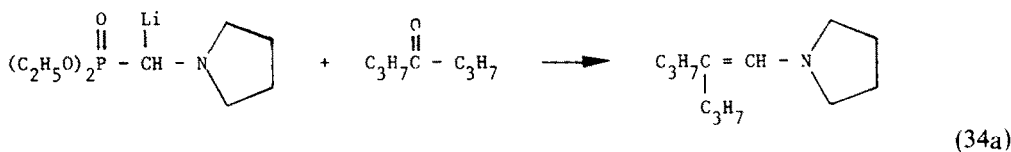


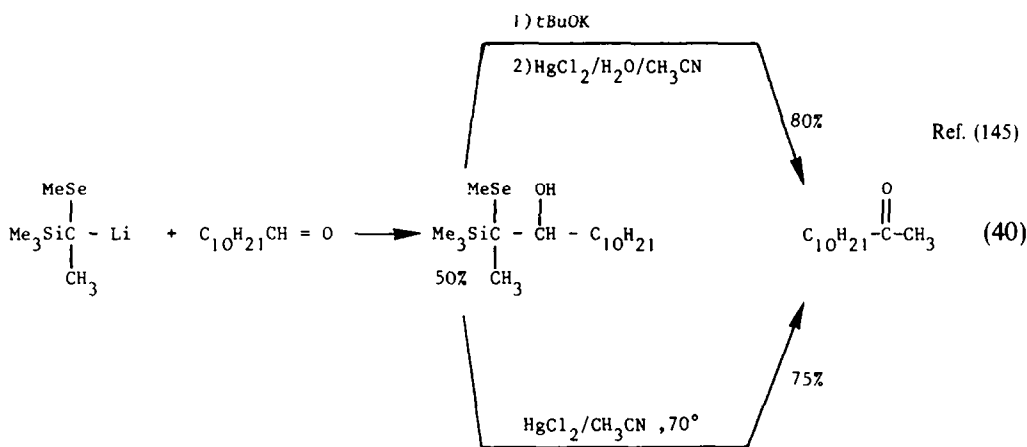
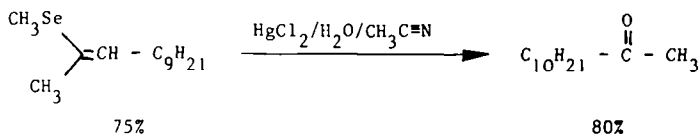
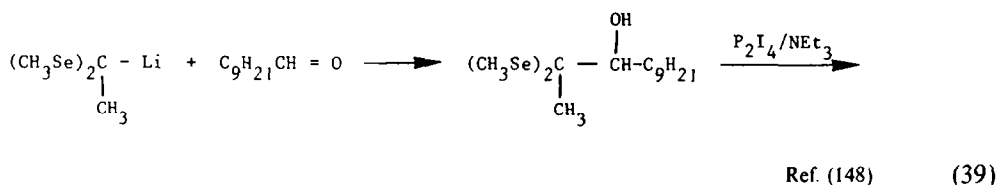
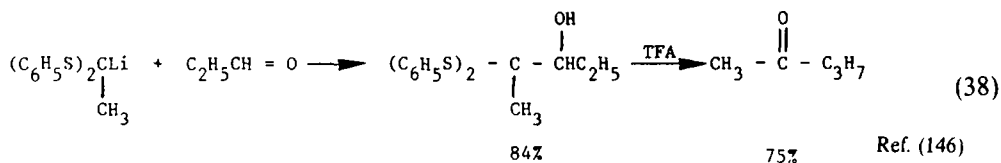
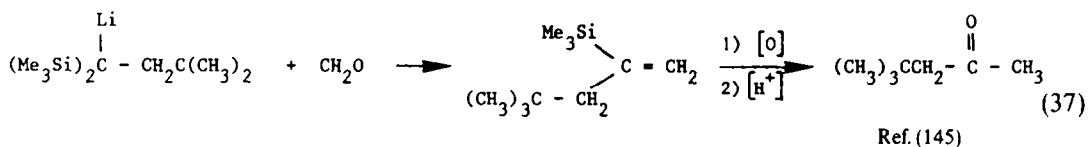
(c) 1-metallo vinyl-ethers,<sup>126-131</sup> -sulfides,<sup>132-134</sup> -selenides<sup>109,136</sup> and 1-lithioimines<sup>137,138</sup> (Eqs. 30-33).



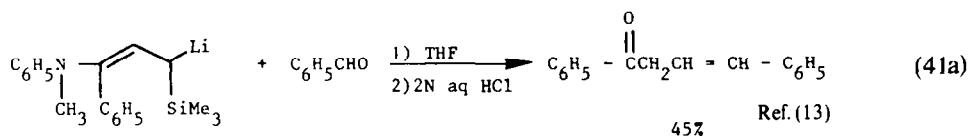


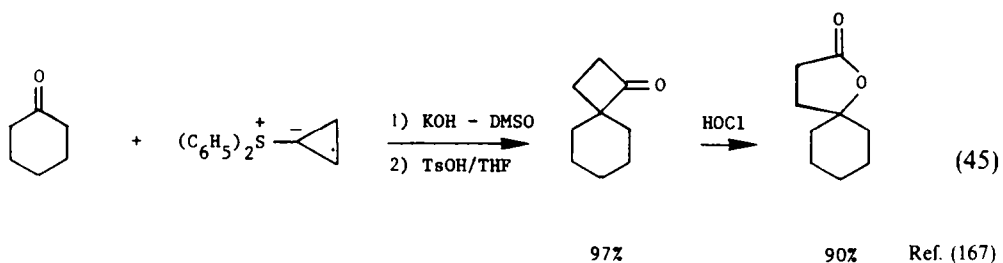
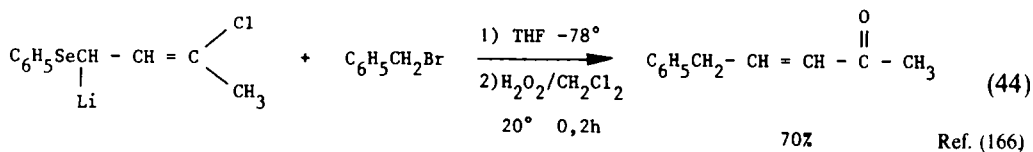
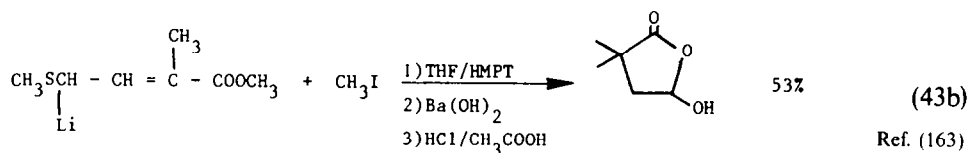
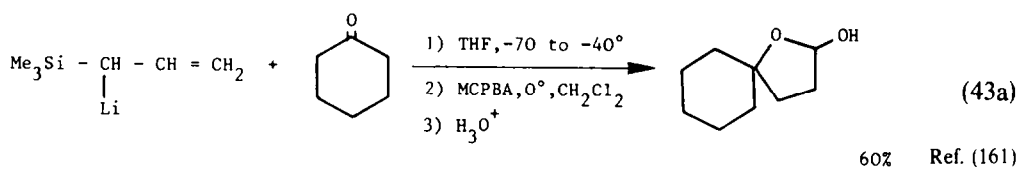
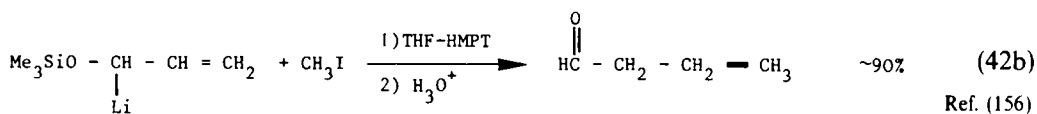
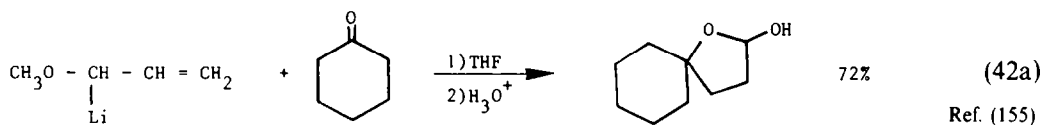
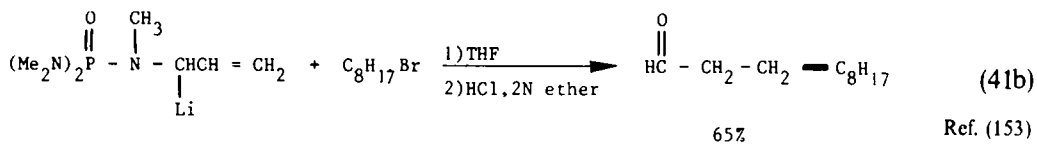
5. The homologization of carbonyl compounds via  $\alpha$ -lithio-phosphonates,<sup>133,140,141</sup> -phosphinonoxides,<sup>142,143</sup> -phosphonium,<sup>133</sup> sulfur ylides,<sup>62</sup>  $\alpha$ -lithio-bis (silyl)alkanes,<sup>145</sup>  $\alpha$ -lithio dithioalkanes,<sup>51,146,147</sup>  $\alpha$ -lithio diselenoalkanes,<sup>57,148</sup>  $\alpha$ -lithio  $\alpha$ -silyl selenides<sup>115</sup> (Eqs. 34–40),  $\alpha$ -sodio chloroesters<sup>78</sup> (Eq. 16) and  $\alpha$ -metallo nitroalkane.<sup>135,139a\*,c\*</sup>



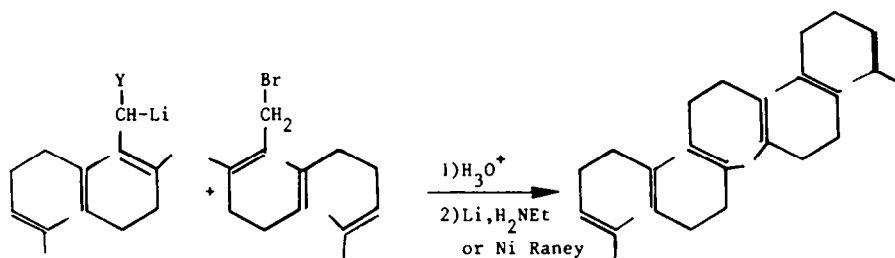


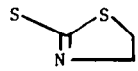
6. The synthesis of carbonyl compounds from masked homoenolates equivalents such as  $\alpha$ -metallo allylamines,<sup>13\*, 149-154</sup>  $\alpha$ -metallo allylethers,<sup>155-159</sup>  $\alpha$ -lithio allylsilanes,<sup>160, 161</sup>  $\alpha$ -lithio allylsulfides,<sup>25\*, 159, 162-164</sup>  $\alpha$ -lithio allylsulfones,<sup>165</sup>  $\alpha$ -lithio allylselenides<sup>166</sup> as well as cyclopropylidene diphenylsulfurane<sup>167</sup> (Eqs. 41-45).

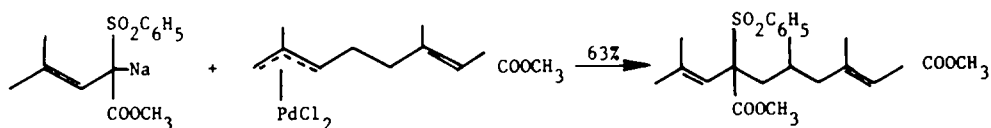




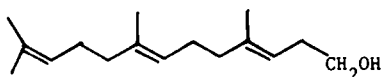
7. The regio and stereoselective synthesis of 1,5 dienes from allylhalides and allylphosphoranes,<sup>168</sup>  $\alpha$ -lithio allylsulfides<sup>169-171</sup> and  $\alpha$ -lithio allylsulfone<sup>172-174</sup> (Eqs. 46-47).



Y :	overall	Ref.	(46)
SC <sub>6</sub> H <sub>5</sub>	56%	(169)	
	35%	(171)	
SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	69%	(172)	
P(nBu) <sub>3</sub>	65%	(168)	



1) LiI, NaCN, DMF Ref. (174)  
 2) Dibal  
 3) Li, H<sub>2</sub>NEt  
 (47)



33%

The choice of a specific heterosubstituted carbanion among the numerous able to perform one of these transformations will of course depend on its availability (including the ease of preparation of its precursor), its stability, its nucleophilic (compared to its basic) behaviour, and the ease with which the heteroatomic moiety will be further selectively removed.

The first chapter will present generalities about the relative stabilization of the carbanionic center in these intermediates, the implications of the cation and of the solvent both for their preparation and their use (Chapter IA). We will further discuss the reactivity of some  $\alpha$ -heterosubstituted organometallics toward  $\alpha$ -enones which show ambident C<sub>1</sub> or/and C<sub>3</sub> reactivity (Chapter IB).

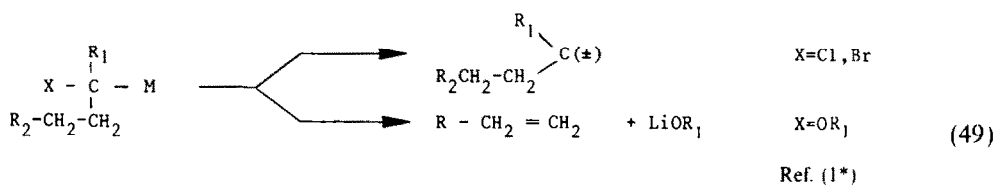
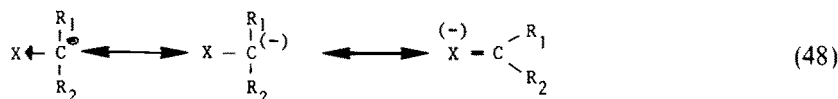
The second chapter will disclose some valuable routes to  $\alpha$ -heterosubstituted organometallics; it will be restricted (except in the case of the metallation reaction) to derivatives which bear *only one non charged heteroatomic moiety and hydrogen(s) or alkyl group(s) on the carbanionic center*. These are usually the more difficult to synthesize.

The third and last chapter will present in more details the reactivity of  $\alpha$ -selenoalkyllithiums toward electrophiles and the possible transformations of the formed adducts.

## CHAPTER I

IA.  $\alpha$ -HETEROSUBSTITUTED ORGANOMETALLICS STRUCTURE-EASE OF SYNTHESIS RELATIONSHIPS

The general comments devoted to classical organometallic chemistry apply to the special case of  $\alpha$ -heterosubstituted organometallics. The heteroatom will of course introduce its own effects which will affect the kinetic of the carbanion formation (relative kinetic acidities), the relative stabilization of the carbanionic center (relative thermodynamic acidities) (Eq. 48) and the stability of such intermediates (decomposition to carbenes or rearrangements (Eq. 49).

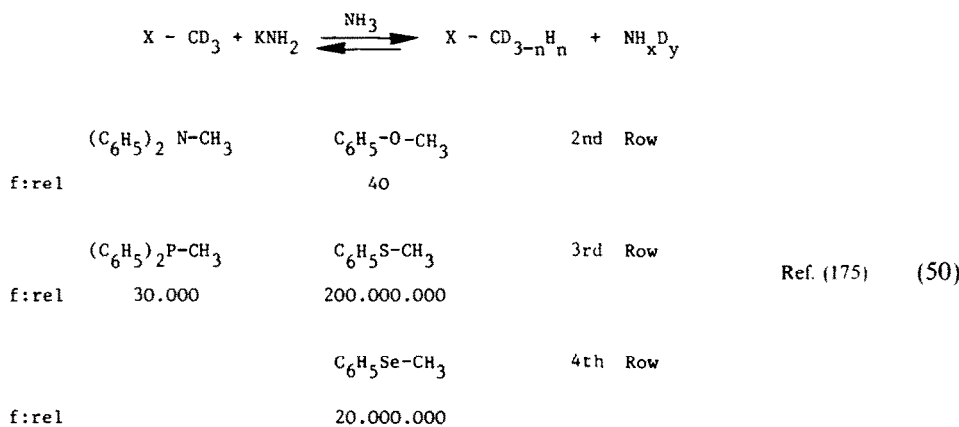


see reference 1\* page 199

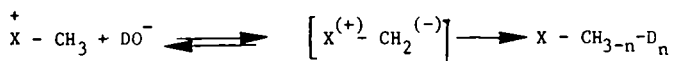
Many of the quantitative results in these fields were obtained via the metallation reaction and this is the subject of the following section.

## IA1 Selected acidities measurements

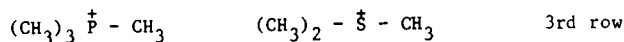
*Kinetic acidity measurements* have been performed on compounds bearing a methyl group directly attached to a non charged<sup>175</sup> (Eq. 50) or a charged<sup>176</sup> (Eq. 51) heteroatom as well as on a series of  $\alpha$ -dithioalkanes<sup>177</sup> (Eq. 52),  $\alpha$ -trihalogenoalkanes<sup>180</sup> (Eq. 54).



f: ratio of the deuterium exchange rate for a given C-D bond in compound compared to another one, each one being related to C-D rate exchange on benzene.



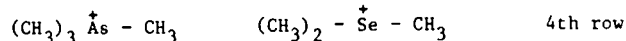
(0)



(94.7)

(125.6)

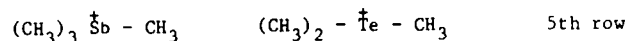
Ref. (176)



(9.5)

(16.9)

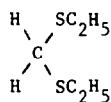
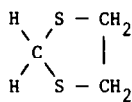
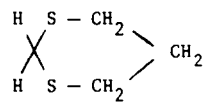
(51)



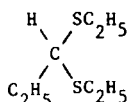
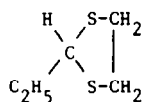
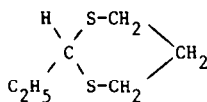
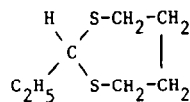
(1)

(4.1)

(Relative deuterium content)

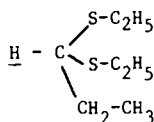
1a (40)2a (516)3a (214)

Ref. (177)

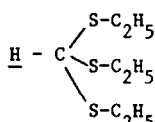
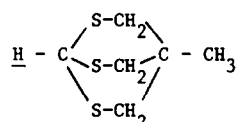
1b (1)2b (19)3b (1.55)4b (5.37)

(52)

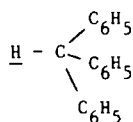
(Relative rate of exchange of tritiated compounds with tbuOK/tbuOH system at 120° for 24 hrs.)



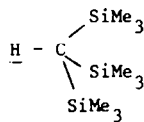
relative rate\* : (1)

(14.8 10<sup>3</sup>)(17.8 10<sup>6</sup>)

Ref. (177)



relative rate\*\* : (1)



(5-7)

(53)

\* relative rate of exchange tbuOK/tbuOH/120°/24 hrs (177,178)

\*\* relative rate of exchange KOH/DMSO-H<sub>2</sub>O/50° (179)



$(C_2H_5O)_3CH$	$F_3CH$	
(0,00000006)	-	
$(C_2H_5S)_3CH$	$Cl_3CH$	
1	(>5000)	
	$Br_3CH$	
	(>60.000)	
	$I_3CH$	
	(>60.000)	
		Ref. (180a)

(54)

(relative rate of exchange in KOH ethanol/water 80/20 at 35°)

	$F_3CH$	$Cl_3CH$	$Br_3CH$	$Cl_3H$	
pK*	28 - 31	15.5	13.7	13.7	(180b)

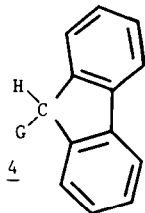
\* compared to  $ClI_2$  (pK = 40) in DMSO/ $CD_3OD$  50/50 +  $NEt_3$  (catalyst)

*Thermodynamic acidities* were in some cases described. Bordwell<sup>181-183</sup> generally uses DMSO as solvent ( $\epsilon = 49$  at 20°; Eqs. 55-58) whereas Streitweiser<sup>184</sup> performs the measurements in cyclohexylamine, reacting the cesium salt of suitable indicator hydrocarbons such as 9-phenylfluorene, or triphenyl methane (Eq. 59).

	<u>1</u>	pK *		<u>2</u>	pK	
a	$CH_3SO_2C_6H_5$	29	a	$CH_3-CH_2-SO_2C_6H_5$	31	
b	$CH_3SO_2CF_3$	18.8	b	$CH_3-CH_2-SO_2CF_3$	20.4	Ref. (182)
c	$CH_3NO_2$	17.2	c	$CH_3CH_2NO_2$	16.7	
d	$CH_2(SO_2C_2H_5)_2$	14.4	d	$CH_3CH(SO_2C_2H_5)_2$	16.7	(55)
e	$CH_2(SO_2C_6H_5)_2$	12.2	e	$CH_3CH(SO_2C_6H_5)_2$	14.3	

Under the same conditions  $CH_3C(=O)CH_3$  has a pK of 26.5 and  $C_2H_5C(=O)C_2H_5$  a pKa of 27.1

\* pK determined in DMSO

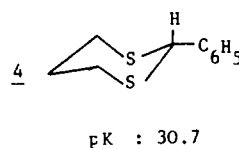
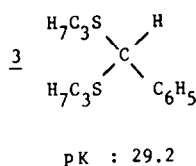
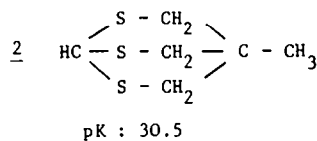
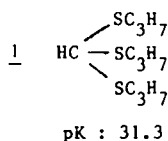
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	
G	$G-CH_2-C\equiv N$	$G-CH_2-SO_2C_6H_5$	$G-CH_2-C(=O)-C_6H_5$		Ref. (181, 182)
a	$CH_3$	32.5 *	31 *	24.4 *	22.3 *
b	$CH_3O$	-	30.7	22.9	22.1
c	$C_6H_5O$	28.1	27.9	21.1	19.9
d	$CH_3S$	-	23.4	-	18
e	$C_6H_5Se$	-	-	18.6	-
f	$C_6H_5S$	20.8	20.5	17.1	17.45
g	$(CH_3)_3N^{(+)}$	20.6	19.4	14.6	17.80
h	$C_6H_5SO_2$	12.0	12.2	11.4	-
i	$NO_2$	-	7.1	7.7	-

\* refers to pK in DMSO

<u>1</u> C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	~45	<u>4</u> C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SC <sub>6</sub> H <sub>5</sub>	30.8		
<u>2</u> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CH <sub>2</sub>	32.3	<u>5</u> (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CH.SC <sub>6</sub> H <sub>5</sub>	26.7	<u>7</u> H <sub>2</sub> C(SC <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	30.8
<u>3</u> (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> CH	30.6	<u>6</u> C <sub>6</sub> H <sub>5</sub> CH(SC <sub>6</sub> H <sub>5</sub> ) <sub>2</sub>	23.0	<u>8</u> HC(SC <sub>6</sub> H <sub>5</sub> ) <sub>3</sub>	22.8

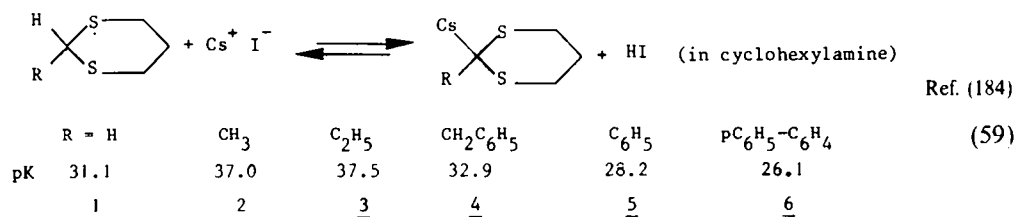
Ref. (182)

(57)



Ref. (182) (58)

Thermodynamic acidity measurements in DMSO



Finally, gas phase acidity measurements, closely related to theoretical calculations, were recently carried out<sup>185</sup> on reasonably stabilized derivatives (Eq. 60) (for the correlation of thermodynamic and gas phase acidity values, see Refs. 183, 185).

	$\Delta G_D^*$	(pK)**		$\Delta G_D^*$	(pK)**
1. CH <sub>3</sub> -SOCH <sub>3</sub>	367.2	(35.1)	-	-	-
2. CH <sub>3</sub> -SO <sub>2</sub> CH <sub>3</sub>	358.9	(31.1)	-	-	-
3. CH <sub>3</sub> -SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	355.3	(29)	7. CH <sub>3</sub> NO <sub>2</sub>	350.7	(17.2)
4. CH <sub>3</sub> CH <sub>2</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	357.2	(31.1)	8. CH <sub>3</sub> CH <sub>2</sub> NO <sub>2</sub>	351.0	(16.7)
5. C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	356.3	-	9. (CH <sub>3</sub> ) <sub>2</sub> CHNO <sub>2</sub>	350.3	(16.9)
6. $\triangle$ CH <sub>2</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	354.9	-			

Ref. (185)

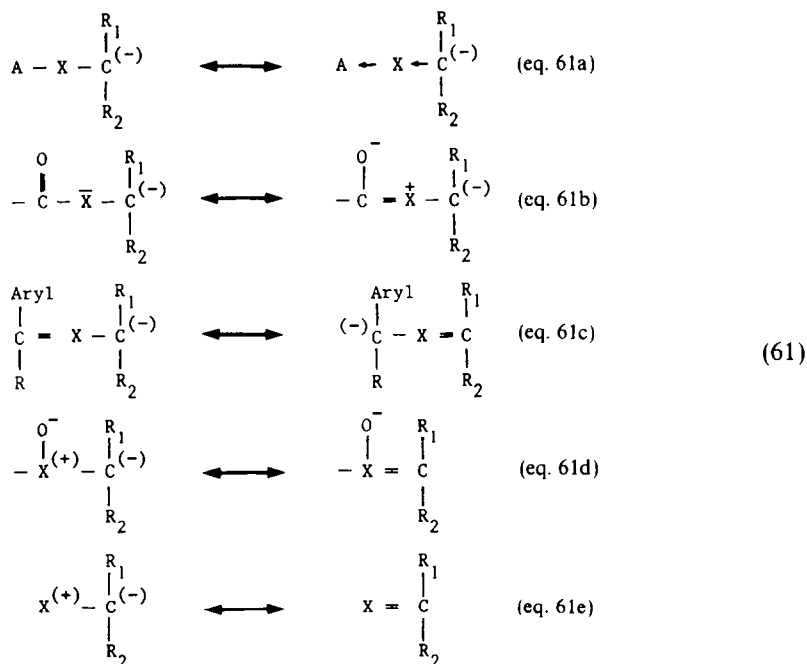
(60)

\* corresponds to free energy change for HA  $\rightleftharpoons$  H<sup>(+)</sup> + A<sup>(-)</sup> in gas phase at 300°K

\*\* refers to pK in DMSO

### IA2 Selected qualitative problems related to $\alpha$ -heterosubstituted organometallics synthesis

The ease of formation of an heterosubstituted organometallic is dependant on the nature of the heteroatom itself but also for a large part on the nature of the heteroatomic moiety and of the other groups directly attached to the carbanionic center (Eq. 61).



Of course, the route chosen (Chapter II) as well as the experimental conditions used will play a crucial role for its successful synthesis.

(a) *All things being equals the synthesis of an organometallic is easier:*

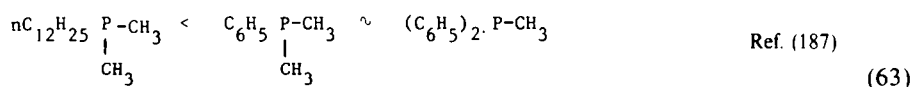
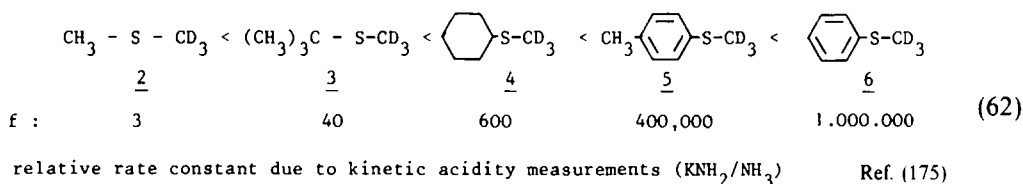
( $\alpha$ ) when the heteroatom is changed by another one which is located at its right in the same row of the periodic table (compare the results of Eq. 50, 51, 54).

( $\beta$ ) when the heteroatom belongs to the third row of the periodic table instead of the fourth or the second row [compare results Eqns 50, 51, 54 and 56, entry f to e and c and also  $(\text{C}_6\text{H}_5\text{S})_2\text{CH}_2$  pH 32-33,<sup>186b</sup>  $(\text{C}_6\text{H}_5\text{Se})_2\text{CH}_2$  pK 35<sup>186b</sup>].

( $\gamma$ ) when the heteroatomic moiety is modified as shown in Eq. (61) and:

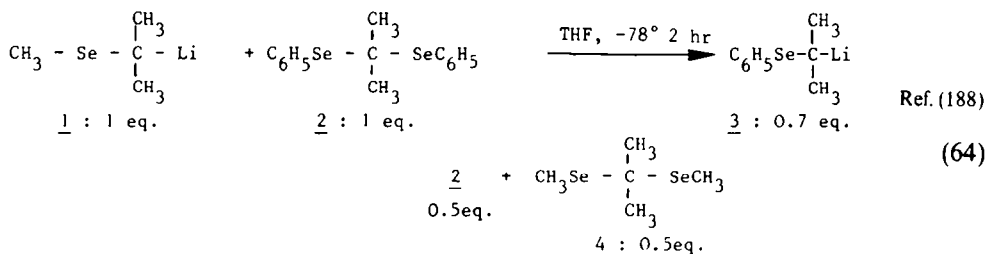
—possesses an attracting group directly attached to the heteroatom (Eq. 61a). Among these, the phenyl group and the trifluoromethyl one (Eq. 55, compare **1b** to **1a**) are well known dramatically enhance the acidity of the derivatives when directly attached to the heteroatom.

The phenyl group (Eq. (62) compare **6** to others, Eq. (63), Chapter IIB1 and Table VII) occupy a place of choice since the related compounds are usually easily prepared.



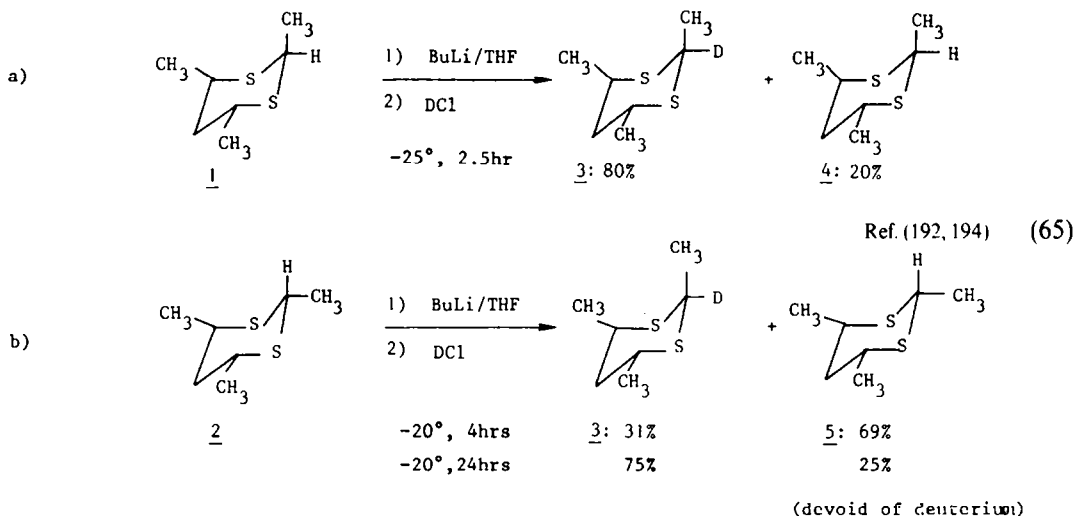
from the ease of metalation using BuLi-TMEDA as base in hexane

The formation<sup>188</sup> of 2-lithio-2-phenylselenopropane **3** from 2,2-bis(phenyl-seleno)propane **2** and 2-lithio-2-methylselenopropane **1** (Eq. 64) can be explained in term of difference of stabilization of the two carbanions **1** and **3** which favor of the latter.



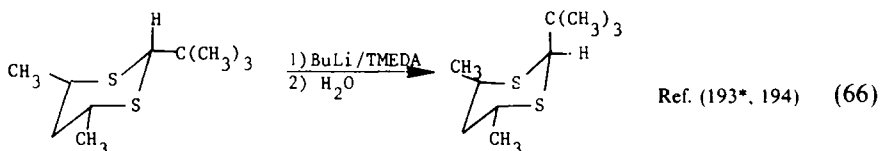
Other quoted examples are listed in Eq. (56)<sup>181, 182</sup> (cf in oxygen cases **2c**, **3c**, **4c** respectively with **2b**, **3b**, **4b**; in sulfur case **2f**, **4f** respectively with **2d**, **4d**),

- can stabilize the carbanionic centre, by charge dipole interaction<sup>10\*</sup> (Eq. 61b). This effect explains the easiest synthesis  $\alpha$ -alkoxy,  $\alpha$ -amino,  $\alpha$ -thio carbanions when the alkyl group is replaced by a mesityl group,<sup>10\*</sup> and the successful metallation of phosphonamides,<sup>10\*</sup> nitrosamines,<sup>11\*</sup> isonitriles<sup>12\*</sup> (see Chapter IIB1 and Table VII).
- can delocalize the negative charge as in carbanions derived from benzaldimines (Eq. 61c, see Chapter IIB1 and Table VII).
- bears a partially charged or fully charged heteroatom (Chapter IIB1, Table VII) such as in phosphonyl<sup>16\*</sup> or phosphonate,<sup>9\*, 17\*</sup> sulfinyl, arsinyl, seleninyl carbanions and related; in  $\alpha$ -metallo sulfones,<sup>26\*, 27\*</sup> and sulfoximines;<sup>69\*</sup> in  $\alpha$ -metallo nitroalkanes<sup>189\*, 190\*</sup> (Eq. 61d), in phosphorus-,<sup>9\*, 18\*, 22\*</sup> sulfur-,<sup>9\*, 23\*, 28\*</sup> arsenic-,<sup>9\*</sup> selenium-,<sup>68</sup> and stilbonium-ylides<sup>9\*</sup> (Eq. (61e); [cf. for example Eq. (56) **1f**, **2f**, **3f** to **1h**, **2h**, **3h**: Eq (60); **1to 2**].
- is part of a 5- of 6-membered cycle as in 1,3-dithianes or -trithianes compared to the open chain analogues (Eqs. 52, 53) (for a contradictory report: cf Eqs. 58–59).
- Eliel<sup>191–194, 195\*</sup> recently described the highly selective abstraction of the equatorial hydrogen in conformationally fixed 1,3-dithianes (Eq. 65).

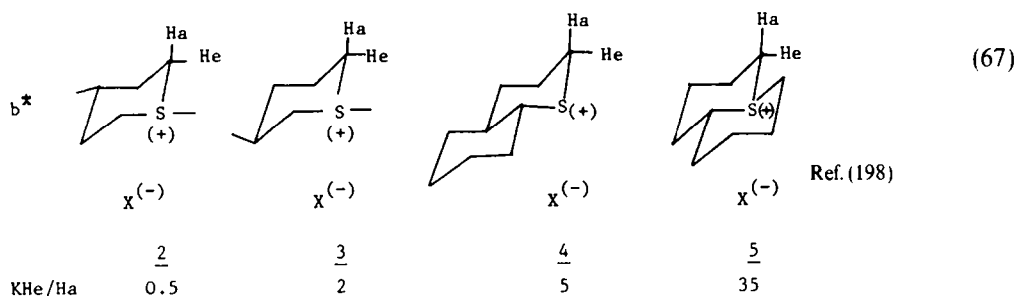
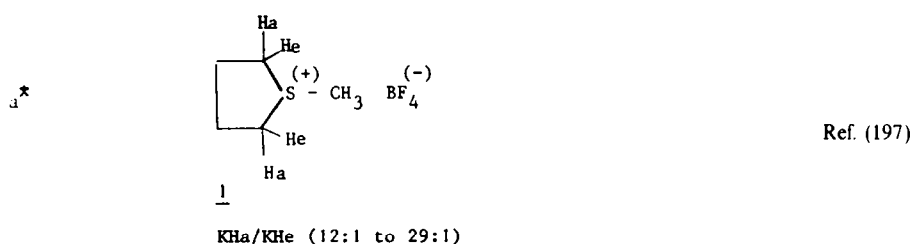


Related to these observations is the ease with which the equatorial hydrogen in 2-methyl dithiane (**1**, Eq. 65) is metallated by *n*BuLi in THF and the difficulties encountered to apply this reaction to its axial isomer (**2**, Eq. 65).<sup>192, 194</sup>

If the resulting organometallics are deuterolysed, hydrolysed or alkylated, the electrophile always lies in the equatorial position (Eq. 65). This allows the synthesis of the less stable axial 2-alkyl-1,3-dithianes<sup>192, 194</sup> (**3**, Eq. 65) and permits the isomerization<sup>193\*, 194</sup> of the very bulky *t*-butyl group from the equatorial to the axial position in a contrathermodynamic process (Eq. 66) (driving force estimated: 6 kcal/mol).

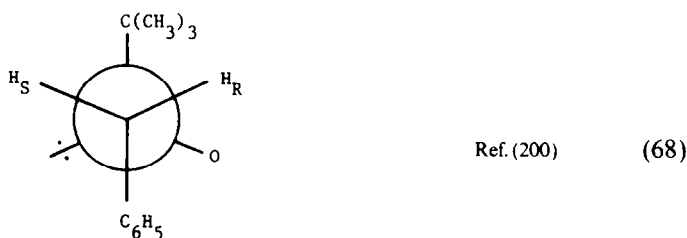


These results suggest a thermodynamic preference for the equatorial orientated carbon—lone pair in 2-lithio 1,3-dithianes<sup>191-193\*,196</sup> whatever the organometallics exist as ions pairs or as anions.<sup>195\*,196</sup> Similar selectivity in proton abstraction was also observed for 5-<sup>194,197</sup> and 6-<sup>198</sup> membered sulfonium salts (Eq. 67) and in the last cases the  $H_e/H_a$  ratio for proton abstraction increases as the ring becomes more rigid (Eq. 67, cf **5** to **2**).

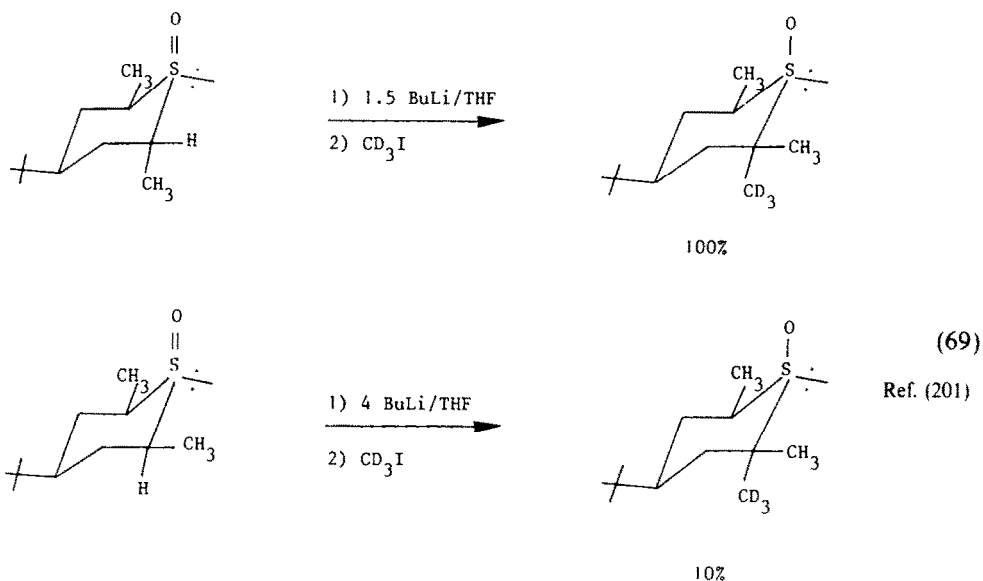


\* kinetic acidity measurements : NaOD/D<sub>2</sub>O (2M or 5M), 60°C.

—We must finally mention the special cases of sulfoxides and sulfones. Durst<sup>199</sup> found that in benzyl-*t*-butylsulfoxide the “pro S” hydrogen, which is assumed to lie anti to the S—O bond in the preferred conformation,<sup>200</sup> is more easily removed by methyl lithium (whose  $pK$  is 13 units higher) in THF at  $-60^\circ$  than the “pro R” one ( $H_S/H_R > 100$ ) (Eq. 68).



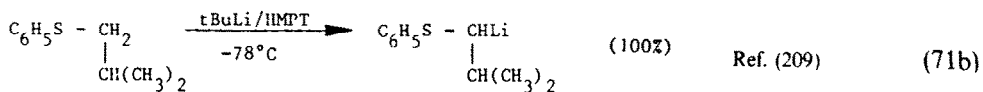
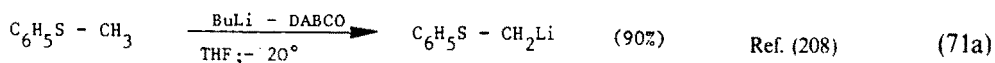
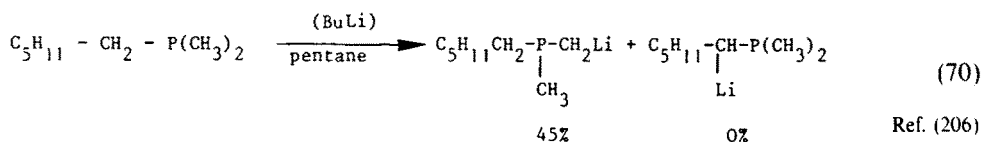
Very high selectivity in removal of the hydrogen *cis* to the S—O bond was observed by Marquet<sup>201</sup> in rigid sulfoxides (Eq. 69) but usually the metallation rate and the relative acidity of the  $\alpha$ -hydrogens are highly dependant on the nature of the solvent used.



It is also well known that  $\alpha$ -sulfonyl carbanion can be generated in an asymmetric form and retains its asymmetry under a variety of conditions.<sup>27\*, 202-204</sup> Among the different conformations possible it was found that the pyramidal carbanion with the lone pair bisecting the O-S-O angle is the more favoured one.<sup>205</sup>

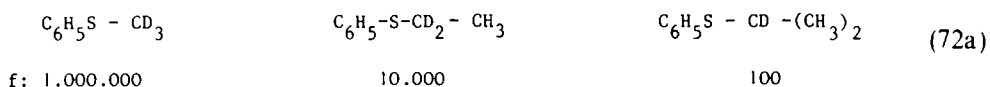
(b) *The nature of the group directly attached to the carbanionic center play of course a crucial role in the stabilization of the carbanionic center.*

— The presence of alkyl groups on the carbanionic center greatly lowers the stabilization of the carbanionic center (pK increased by ~2 units). For example, hexyl dimethyl phosphine is specifically metallated on the methyl group<sup>187, 206, 207</sup> (Eq. 70) and, whereas methyl phenylsulfide is smoothly metallated<sup>208</sup> by BuLi-DABCO (THF, -20°) (Eq. 71), isobutyl phenylsulfide requires<sup>209</sup> the use of strongly basic t-BuLi/HMPT (THF, -78°) (Eq. 71).

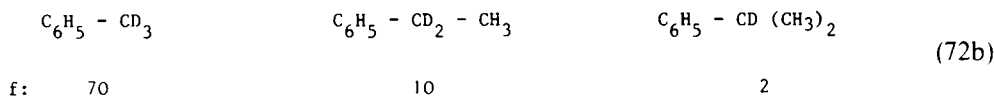


The effect of the alkyl group substitution is quantitatively observed in sulfides by kinetic acidity measurements<sup>175, 177</sup> (Eq. 72a) and in sulfones<sup>182, 185</sup> (cf: eqn (55); **1a** to **2a**; **1b** to **2b**; **1c** to **2c**; and eqn (60); **3** to **4** and **5**) and in dithianes<sup>184</sup> (cf Eq. (59); **2** and **3** to **1**) by thermodynamic acidity measurements.

Surprisingly alkyl substitution has a much more pronounced effect in phenyl sulfides than in alkyl benzenes<sup>175</sup> (cf Eqs. 72a and 72b).



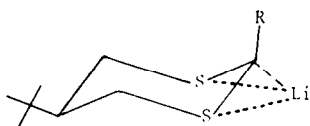
Ref. (175)

kinetic measurements with  $\text{KNH}_2/\text{NH}_3$  system

-- At the opposite the presence of another heteroatom directly attached to the carbanionic center or of an anion stabilizing group such as a phenyl, enyl, ynyl or a carbonyl group (aldehyde, ketone, ester) or a nitrile group greatly enhances the stabilization of  $\alpha$ -heterosubstituted carbanions. Quoted examples are presented in Eqs. 56- 59.

### IA3 How are explained the different behaviour of heteroatoms to stabilize a carbanionic center?

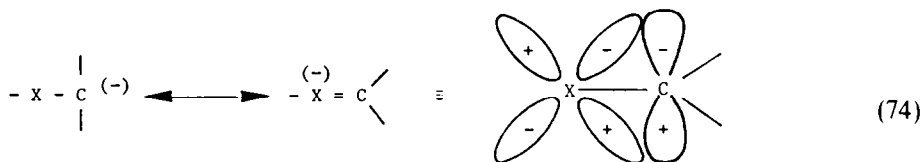
(a) The differences observed when the heteroatoms lie in the same row of the periodic table were explained by the different inductive effects of the heteroatom<sup>175,176,180-182</sup> (Eqs. 50, 51, 54). The repulsions of the non bonding electrons of the heteroatom with the carbanionic center was taken in account to explain the difficult synthesis of  $\alpha$ -fluoro carbanions. The cooperative effect between the unshared electrons of the heteroatoms and the metal cation (Eq. 73) was once proposed<sup>192,193\*</sup> to explain the equatorial preference of the C-Li bond in rigid 2-lithio-1,3-dithianes (Eqs. 65, 66) and then rejected by its authors.<sup>194</sup>



Ref. (192, 193\*, 194) (73)

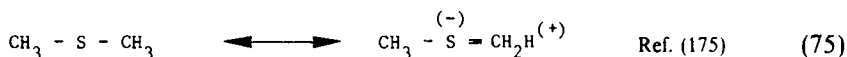
(b) The differences found in derivatives in which the heteroatoms lie in the same column of the periodic table have been the subject of several controversies between the tenants of the "d orbital theory" and the ones of "the polarization theory".

— The "d orbital theory" explains the highest acidity of compounds bearing heteroatoms possessing 3d or 4d unoccupied orbitals (compared to the ones in which the heteroatom lies in the 2nd row of the Periodic Table) by the stabilization of the carbanion by delocalization of the charge in these relatively low lying orbitals. This allows the carbanion 2p  $\pi$ -heteroatom dxy  $\pi$  overlap (Eq. 74) which should be better with 3d than 4d orbitals.



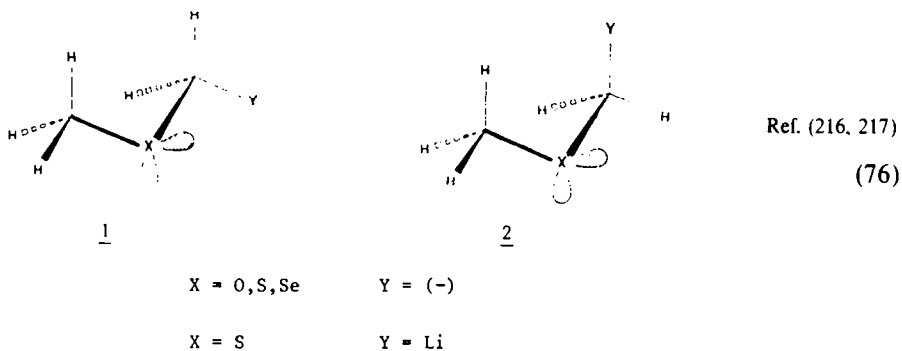
This theory agrees with the different results shown in Eqs. (50), (51), (54), (56). It explains for example the higher acidity of sulfides compared to selenides or ethers (Eq. 50),<sup>175</sup> the higher pK of  $\alpha$ -phenylthioacetophenone compared to its phenylseleno or phenoxy analogues (Eq. (56), entry f to e and c) and the higher acidity of thioacetals compared to selenoacetals.<sup>186</sup>

It is admitted<sup>210</sup> that the d orbitals contract themselves and lower their energy when attached to electronegatives atoms (cf Table VIIC, entry e-i to a-c) or attached to groups such as the phenyl one<sup>182,187</sup> (see Table VII; for the only exception, see Table VIIC, entry j). Finally the higher acidity of t-butyl-methylsulfide compared to dimethyl sulfide was explained<sup>175</sup> by the hyperconjugation not possible in the former product (Eq. 75).



The “d orbital theory” does not account for the higher acidity of tribromomethane compared to chloro analogue<sup>180</sup> (Eq. 54), for the enhanced kinetic acidity of fixed 1,3-dithianes compared to open chain analogues<sup>177</sup> (Eq. 52) (for controversy report,<sup>182</sup> see Eq. 54) and the kinetic preference for the metallation of the equatorial hydrogen in these derivatives.

The “polarization theory” is mainly related to the results of theoretical calculations which stress the unimportance of the  $d\pi$ - $p\pi$  overlap to explain the higher stabilization of carbanions bearing an heteroatom belonging the second or third row of the Periodic Table. These calculations were performed by Streitweiser,<sup>212</sup> Wolfe,<sup>213, 215\*</sup> Lehn<sup>216, 217</sup> for  $^-\text{CH}_2\text{-SR}$  (R: H or  $\text{CH}_3$ ), Lehn<sup>217</sup> for  $^-\text{CH}_2\text{SeR}$  (R: H or  $\text{CH}_3$ ) and by Wolfe<sup>200, 214</sup> for  $^-\text{CH}_2\text{SOH}$  and  $^-\text{CH}_2\text{SO}_2\text{H}$ . Comparisons with  $^-\text{CH}_2\text{-CH}_2\text{R}$  and with  $^-\text{CH}_2\text{-OR}$  (R: H,  $\text{CH}_3$ ) were performed by these authors and last but not least Lehn and Wipff<sup>216, 217</sup> found that the carbanion stabilization increases in the X:  $\text{CH}_2 < \text{O} < \text{S} < \text{Se}$  series (Eq. 76).



All these authors explain their theoretical results by the polarizability of the heteroatom [related to their electronegativity and their refractive index<sup>180</sup> (Eq. 77)] which allows a better diffusion of the carbanionic lone pair into the carbon framework.

compounds	$\text{H-C}(\text{OC}_2\text{H}_5)_3$ , $\text{HC}(\text{SC}_2\text{H}_5)_3$ , $\text{HCF}_3$ , $\text{HCCl}_3$ , $\text{HCBF}_3$ , $\text{HClI}_3$						
relative rates of exchange	$< 6 \cdot 10^{-8}$	1.0	$< 10^{-10}$	$5 \cdot 10^3$	$> 6 \cdot 10^5$	$> 6 \cdot 10^5$	Ref. (180)
atomic refractive constant	1.64	7.97	1.25	5.97	8.87	13.9	(77)
electronegativity of the heteroatom	3.5	2.5	4.0	3.0	2.8	2.5	

This diffusion seems to be higher<sup>216, 217</sup> when the carbanionic lone pair (or the lithio derivative  $\text{X} = \text{S}, \text{Y} = \text{Li}$ ) is *syn* periplanar to the other carbon-carbon bond as shown in conformation 1 (Eq. 76). This can explain the higher acidity of the equatorial hydrogen ( $\text{Y} = \text{H}$ ) in 1 compared to the axial one ( $\text{Y} = \text{H}$ ) in 2. A related explanation has already been given by Wolfe<sup>215\*</sup> under the appellation “*gauche* effect”.

The polarization theory, as already presented for the “d orbital theory”, explains the higher acidity of derivatives in which the heteroatom belongs to the 3rd compared to 2nd row.

The theoretical results of Lehn<sup>217</sup> which implicate the higher acidity of selenides and selenoacetals respectively compared to sulfides and thioacetals seem to disagree with the experimental observations.<sup>181, 186, 188</sup> However, this theory provides an attractive explanation for the highly selective abstraction of the equatorial hydrogen in rigid 1,3-dithianes<sup>191-194, 196</sup> and for the contrathermodynamic equatorial-axial isomerisation of alkyl groups in such derivatives (Eq. 65) (as a large as *t*-Butyl)<sup>193\*</sup> (Eq. 166).

(c) Finally, we must point out that the carbanion stabilization has a tremendous importance not only for its synthesis (whatever the route chosen) but also on its further reactivity toward

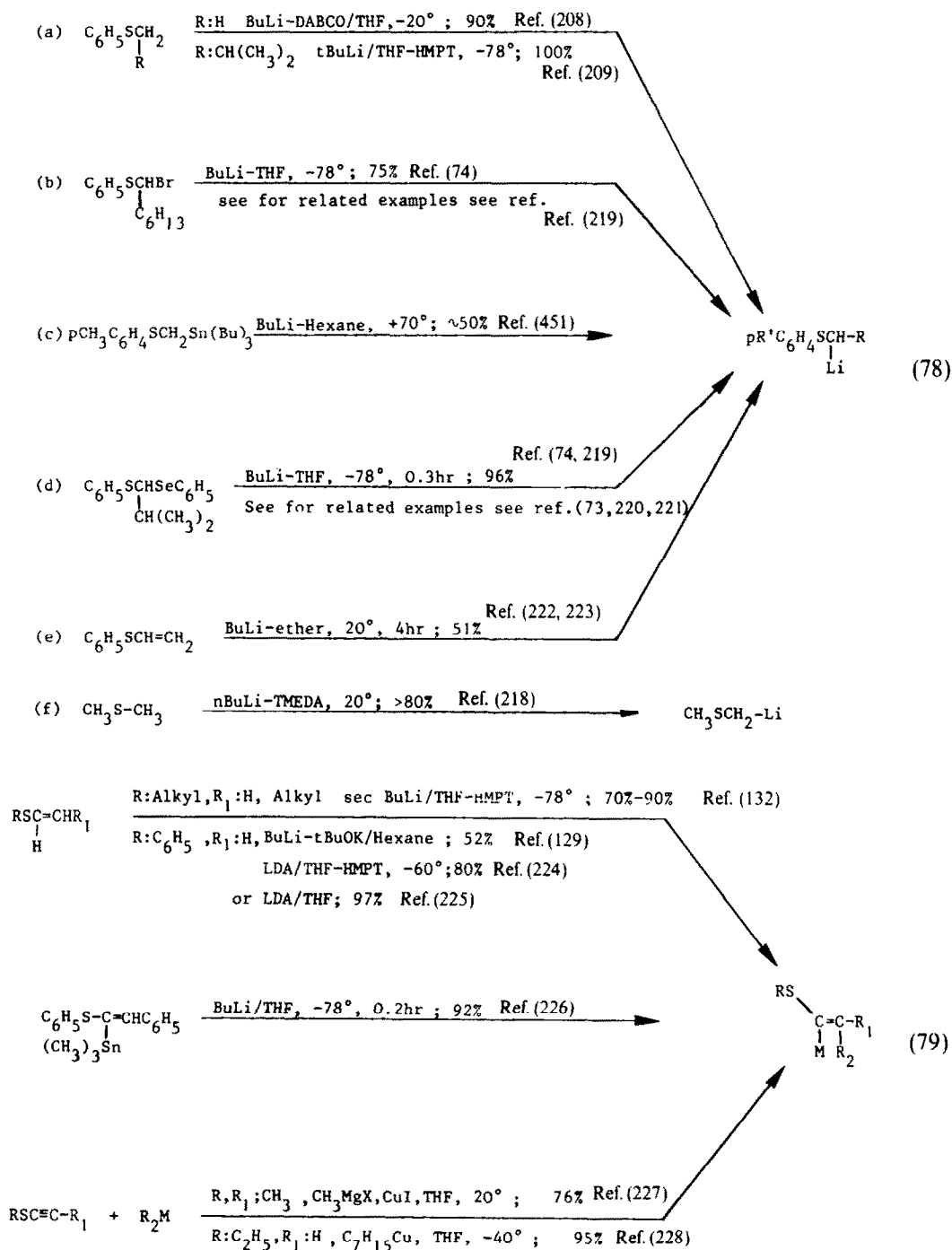


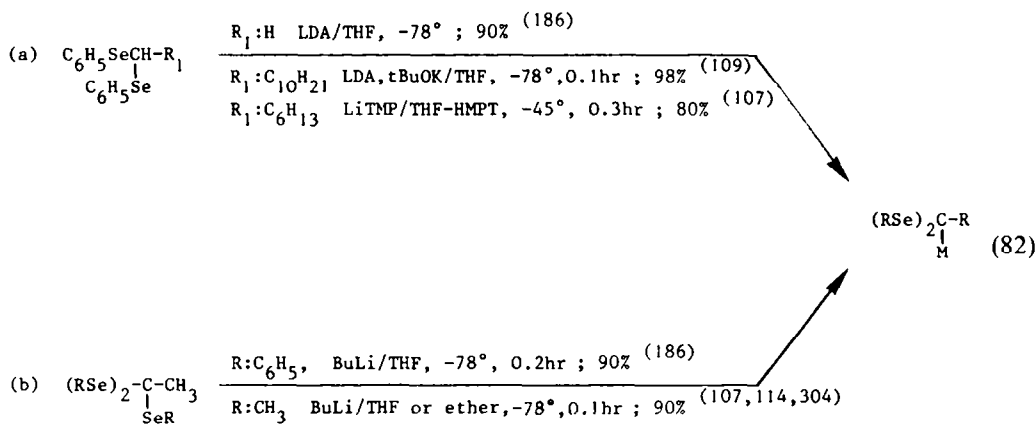
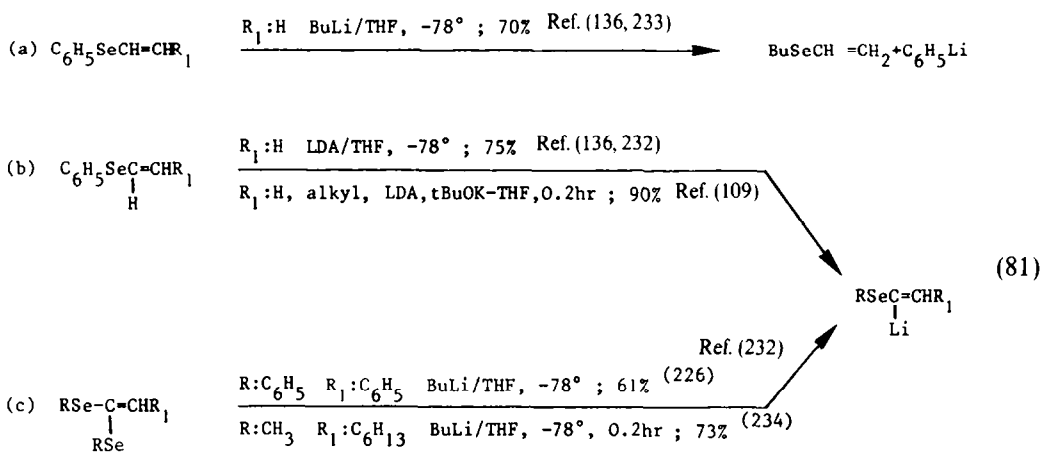
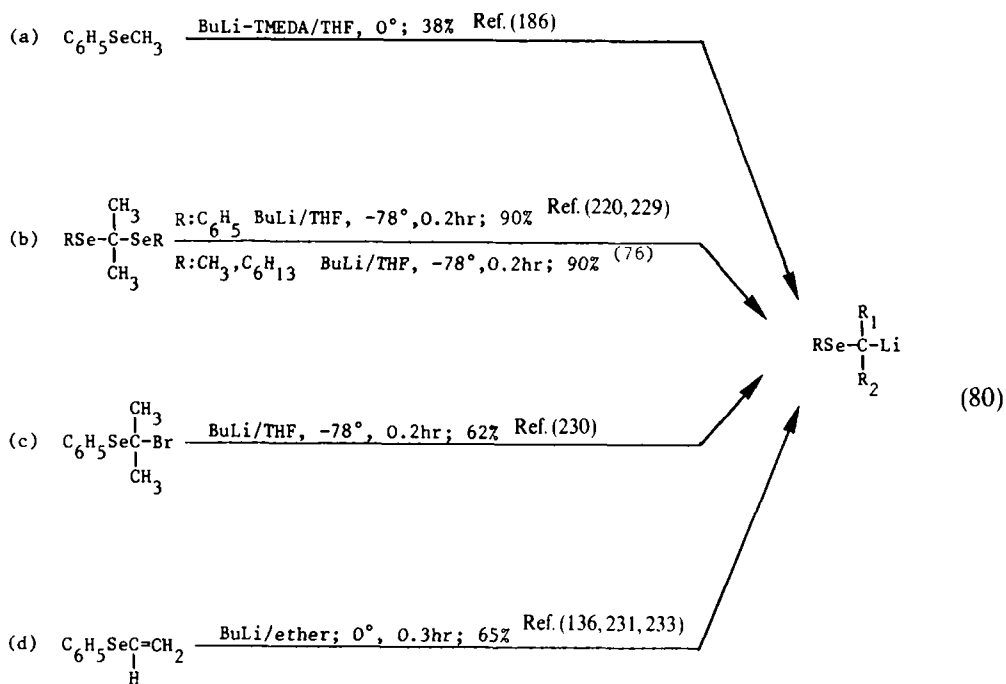
electrophiles. It will modulate its basic/nucleophilic reactivity, its aptitude to react  $C_3$  rather than  $C_1$  with enones (see Chapter II) and the direction of its attack on rigid cyclohexanones.

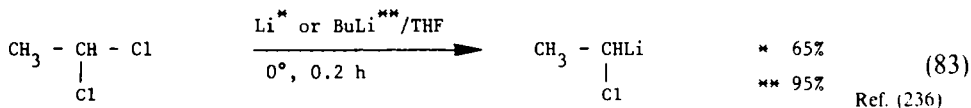
#### IA4 The role of the system used to generate the $\alpha$ -heterosubstituted organometallics

(a) Major work has been carried out with lithium cation, mainly for practical reasons, because of the commercial availability of many alkyllithiums derivatives (from "Metallgesellschaft" in Germany and from "Foote" in the United States) which are frequently used for the synthesis of the desired  $\alpha$ -heterosubstituted organometallics.

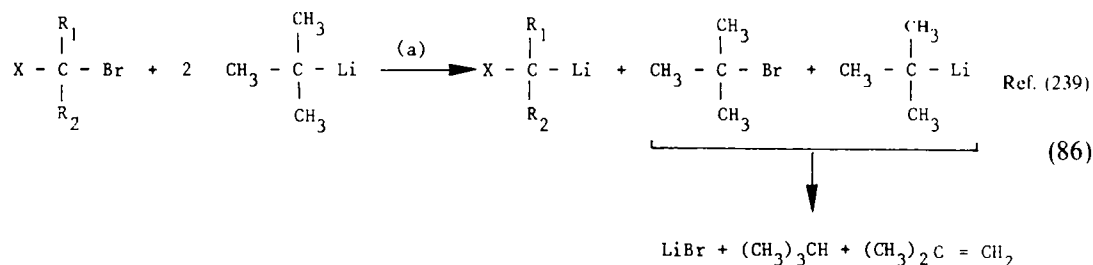
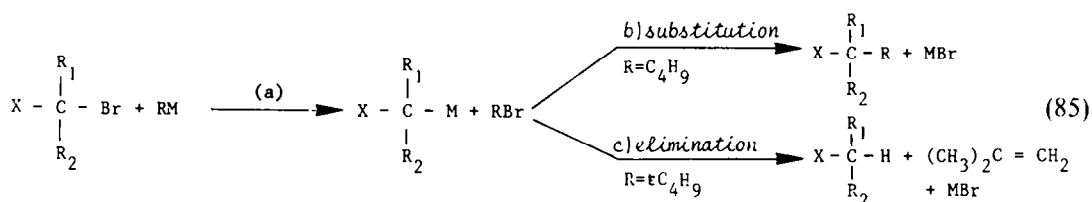
Specific and comparative examples of  $\alpha$ -heterosubstituted organometallics in which the carbanionic center is an  $sp^3$  or an  $sp^2$  carbon atom are presented in the following equations and demonstrate the importance of alkyllithiums and lithium amides for such purposes.





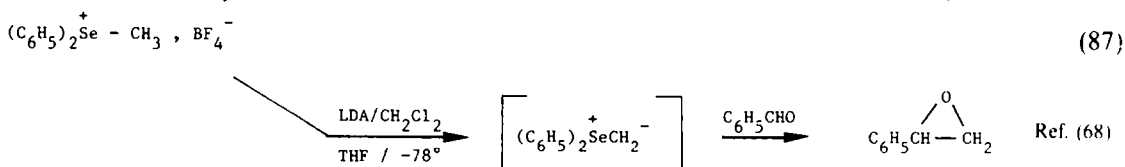
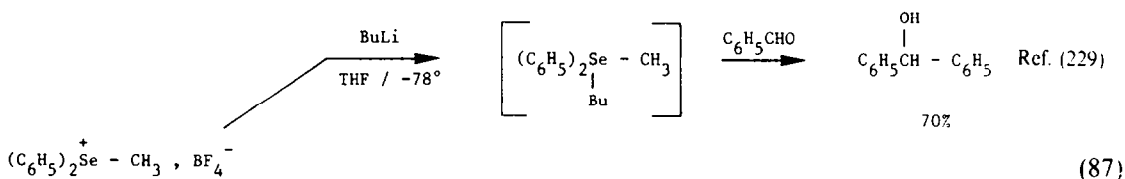


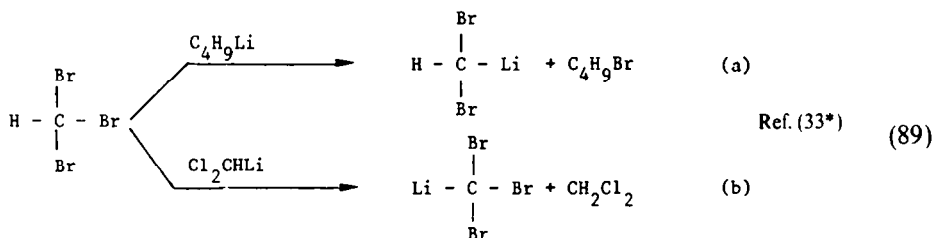
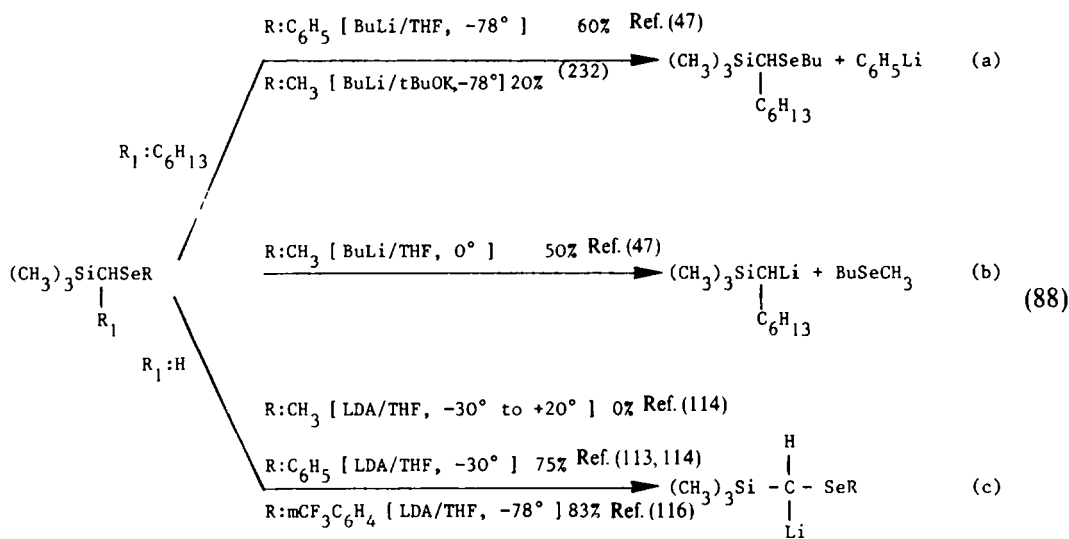
Usually *t*-BuLi is the more reactive alkyllithium known for metallation purposes, for halogen-metal exchange and for selenium-metal exchange; examples follow: isobutyl phenyl sulfide is quantitatively metallated with *t*-BuLi in THF-HMPT at  $-78^\circ$ <sup>209</sup> (Eq. 78) but not with *n*-BuLi under similar conditions<sup>209</sup> and bis(methyl-seleno)alkanes are quantitatively cleaved to the corresponding  $\alpha$ -methylseleno-alkyllithiums at  $-78^\circ$  by *t*-BuLi in ether but not with *n*-BuLi in ether.<sup>61, 238</sup> Use of *t*-BuLi instead of *n*-BuLi should be advantageous in case of halogen-metal exchange reaction because the *t*-Butyl halide formed can be destroyed, if excess of *t*-BuLi (2 eq) is used, preventing thus its further reaction with the  $\alpha$ -heterosubstituted organometallics<sup>239</sup> (Eqs. 85, 86).



Recently, Schlosser introduced *t*-BuLi-*t*-BuOK<sup>129</sup> and trimethylsilyl potassium<sup>240</sup> as very strong basic systems.

The choice of the appropriate basic system is crucial for the success of a reaction. In several instances, alkylmetals are not valuable for metallation purposes since they act as nucleophiles. This is for example the case when carbonyl compounds bearing an alkoxy,<sup>241</sup> amino, silyl,<sup>15\*</sup> thio,<sup>2,32</sup> seleno groups<sup>59</sup> or a chlorine atom:<sup>242</sup> or when sulfonium<sup>28\*</sup> or selenonium salts<sup>68, 229</sup> (Eqn 87a), bis(seleno)alkanes<sup>76, 186, 220, 221, 229</sup> (eqn 80),  $\alpha$ -thioalkylselenides<sup>73, 74, 220, 221</sup> (eqn 78d),  $\alpha$ -trimethylsilyl alkylselenides<sup>47</sup> (eqn 88a, b) or tribromomethane<sup>33\*</sup> (eqn 89a) are reacted with alkyllithiums. In all these cases the organometallic acts as a nucleophile and not as a base, reacting on the carbonyl groups in the first cases and on the sulfur, the selenium or the halogen atoms in the other ones.





Sulfonium,<sup>64</sup> selenonium salts<sup>68</sup> (Eq. 87b) and tribromo methane<sup>33\*</sup> (Eq. 89b) are however successfully metallated with lithio dichloromethane, itself prepared from dichloromethane and lithium diisopropylamine (LDA).  $\alpha$ -Alkoxy,<sup>244</sup>  $\alpha$ -silyl,<sup>15\*</sup>  $\alpha$ -thio,<sup>23\*, 244</sup>  $\alpha$ -seleno,<sup>30\* - 32\*, 245 - 257</sup> carbonyl compounds,  $\alpha$ -(trimethylsilyl)alkylselenides<sup>113, 114, 116</sup> (Eq. 88) and bis(phenylseleno)methane<sup>186</sup> (Eq. 80b) are also easily deprotonated with LDA whereas higher homologs of bis(phenylseleno)methane require the more basic lithium 2,2,6,6-tetramethylpiperidine<sup>107</sup> (LiTMP-Harpon Base)<sup>248</sup> or potassium diisopropylamide<sup>109</sup> (Eq. 82a).

Other valuable bases include N-metallo butyl cyclohexylamine, N-metallo disilyl amide or N-metallo amides (Li, Na, KNH<sub>2</sub>) the last ones are less soluble in organic solvents and are also less bulky.

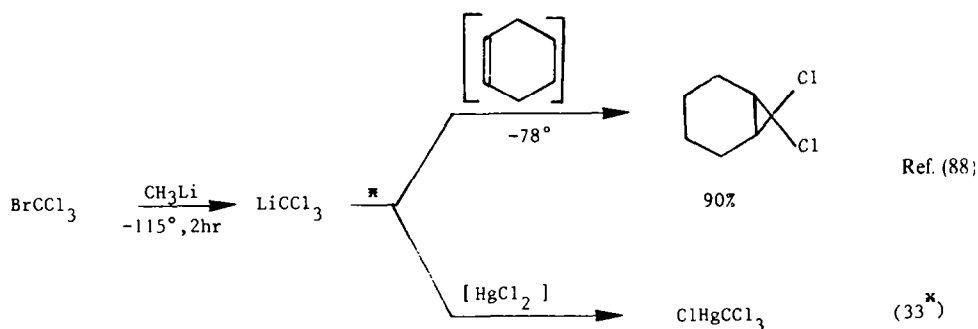
When  $\alpha$ -heterosubstituted organometallics are prepared by halogen-metal exchange directly from metals (i.e. Eq. 83), potassium or sodium are too reactive and are known to produce coupling reactions (Wurtz type). Magnesium is not as reactive and needs a temperature at which the  $\alpha$ -heterosubstituted organometallics often decompose. Lithium is generally reactive enough to avoid both the high temperature and decomposition of the carbanion (Eq. 83)<sup>236</sup> (see Chapter IIB2a and Table VIII A).

(b) *Cation implication for further reaction.* Copper and mercury derivatives of some  $\alpha$ -heterosubstituted organometallics are known and generally prepared by metal-metal exchange from organolithium and copper iodide (CuI) or mercuric chloride (HgCl<sub>2</sub>).

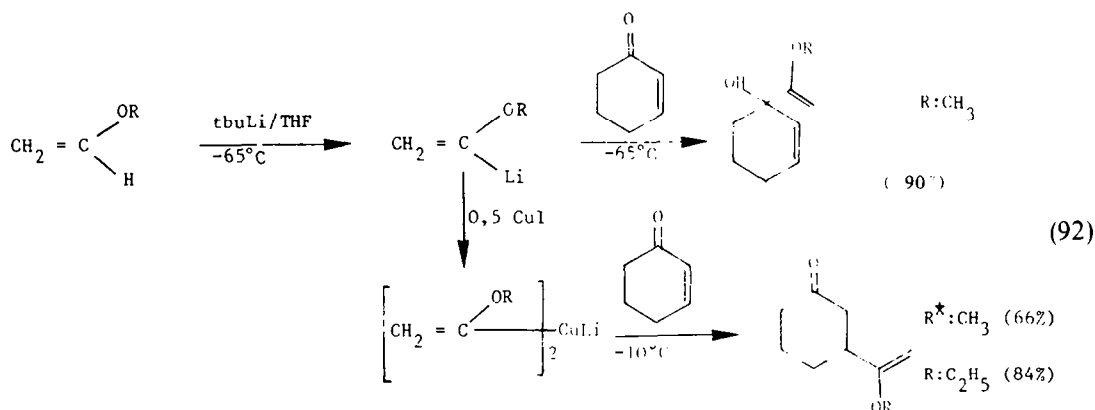
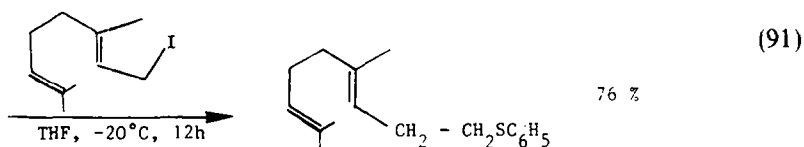
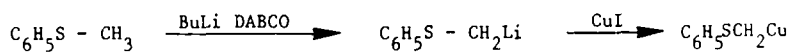
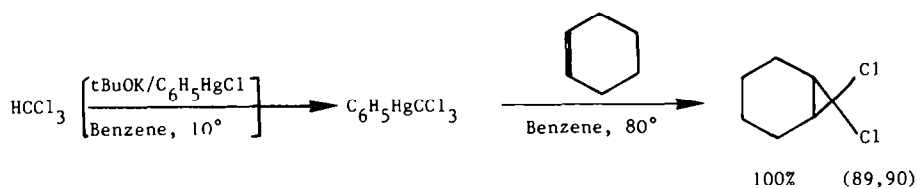
Phenyl trichloromethyl mercury is a stable, easily handled derivative<sup>33\*, 89, 90</sup> whereas trichloromethyl-lithium,<sup>33\*, 88</sup> potassium<sup>249</sup> and ammonium<sup>81\*, 82\*, 83\*</sup> decompose around  $-78^\circ$  producing the corresponding carbene (Eq. 90).

Organolithiums usually react faster with carbonyl compounds than with alkylhalides and reversed reactivity is observed by interchanging lithium by copper cation. Copper derivatives are particularly useful for coupling reaction with allylic halides<sup>250</sup> (Eq. 91).

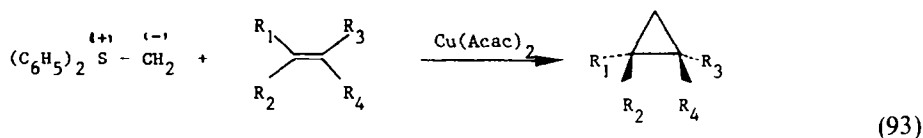
Copper salts are also effective to promote or favor the C<sub>3</sub> addition of organometallics to enones<sup>127, 251, 252</sup> (Eq. 92) and the stereospecific (100%) addition of diphenylsulfoniummethylyde to 2-octenes<sup>253</sup> (Eq. 93) which is uneffective in their absence.



\* If the crude mixture is hydrolysed  $\text{CHCl}_3$  (65%) and  $\text{CHBrCl}_2$  (11%) are isolated (90)



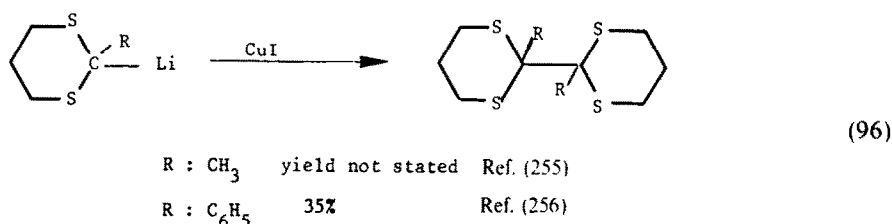
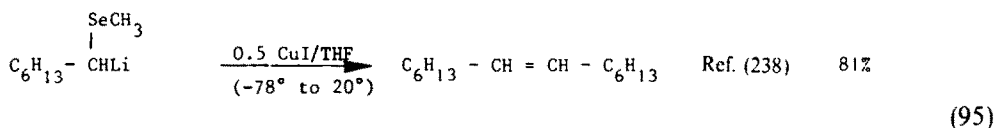
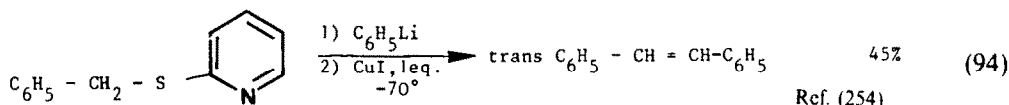
\*  $\text{CH}_3\text{SCH}_3$  was found necessary



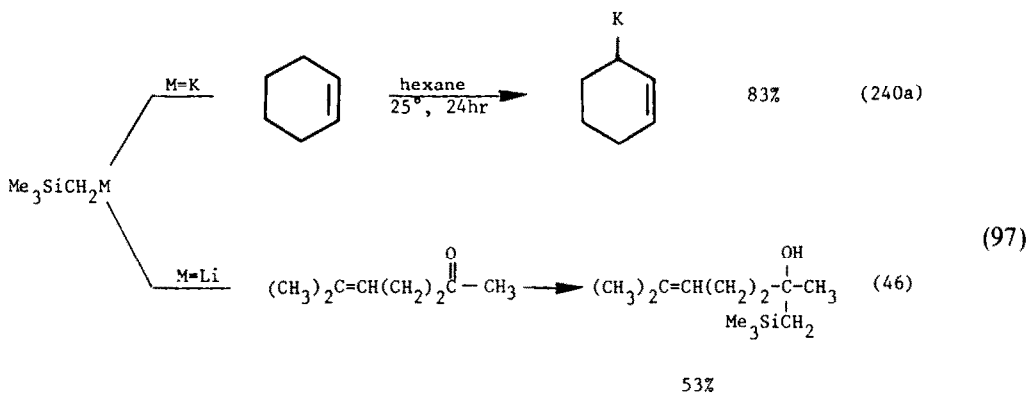
$\text{R}_1 : \text{CH}_3 ; \text{R}_2 : \text{H} ; \text{R}_3 : \text{H} ; \text{R}_4 : \text{C}_5\text{H}_{11} \quad 48\%$

$\text{R}_1 : \text{CH}_3 ; \text{R}_2 : \text{H} ; \text{R}_3 : \text{C}_5\text{H}_{11} ; \text{R}_4 : \text{H} \quad 41\%$

In several instances however, oxidative coupling of the carbanion<sup>238,254-256</sup> occurs exclusively on addition of copper iodide (Eq. 94-96).



On the other hand, the potassium cation usually increases the basicity of the carbanion,<sup>46,240</sup> specific examples are shown in the following equations (Eq. 97).



And finally the cation is known to have a great implication in controlling the stereochemistry of the formed olefin in the wittig reaction<sup>41</sup> (Eq. 3).

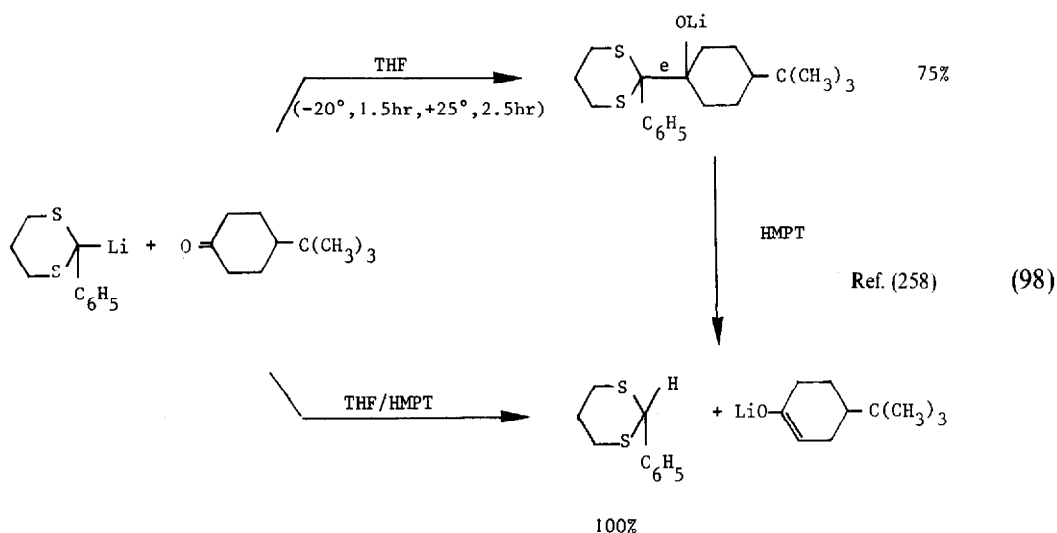
#### IA5 The role of the solvent for $\alpha$ -heterosubstituted organometallics synthesis

The nature of the solvent has an important influence<sup>257\*</sup> on the nature of organometallics in solution (polymers, dimers, monomers) and on the ionisation and the dissociation of the carbon metal-bond.

Ionisation is related to the basicity of the solvent and the dissociation is influenced by its dielectric constant.

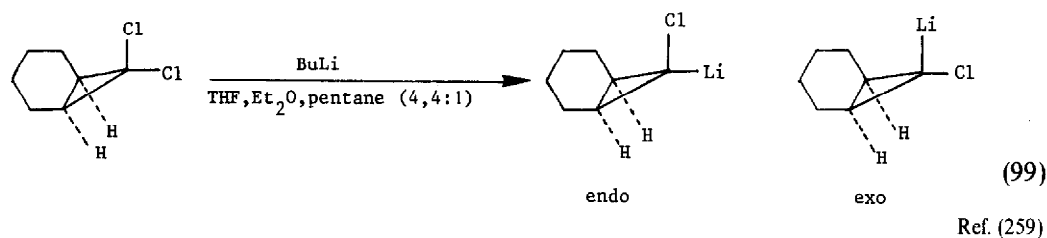
For instance, Eliel<sup>196</sup> suggested that 2-phenyl 2-lithio 1,3-dithiane exist as tight ion pair in THF or cyclohexane and as solvent separated delocalized ion pair in HMPT. Basic reactivity is enhanced when basic solvents with chelating properties such as hexamethyl phosphotriamide (HMPT) or when chelating agents such as tetramethylethylenediamine (TMEDA), crown ethers or cryptands are

added. However as the solvent has an implication in the synthesis of the carbanion and also for its further reactivity, it should be safe to adjust the basicity of the medium to *allow the synthesis* of the desired organometallic but to *avoid a too basic medium* which increases the basicity of the carbanion at the expense of its nucleophilicity<sup>258</sup> (Eq. 98).



(a) *Solvent implications for the synthesis of carbanions.* Hydrocarbons are particularly interesting solvents because of their inertness towards carbanions; unfortunately only few reactions proceed in this medium. Ethers are the most widely used; diethyl ether ( $\text{Et}_2\text{O}$ ), the more basic tetrahydrofuran (THF), the more chelating dimethoxy ethane (DME) or formaldehyde dimethyl acetal (methylal) are valuable representatives.

Other solvents used include a mixture of THF diethyl ether and pentane (4:4:1), "the Trapp Solvent" proposed by Köbrich<sup>259</sup> and Trapp.<sup>33\*</sup> Its low viscosity even at  $-110^\circ$  makes it particularly suitable for low temperature reactions. This solvents system permit the use of some unstable organometallics<sup>259</sup> which decompose or isomerise at temperature higher than  $-110^\circ$  (Eq. 99).

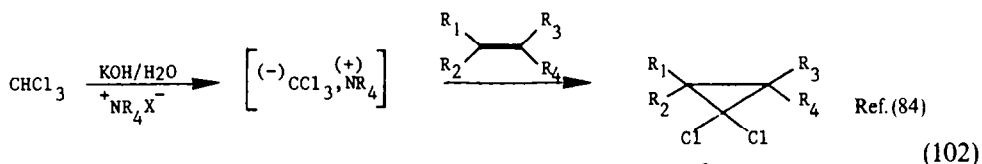
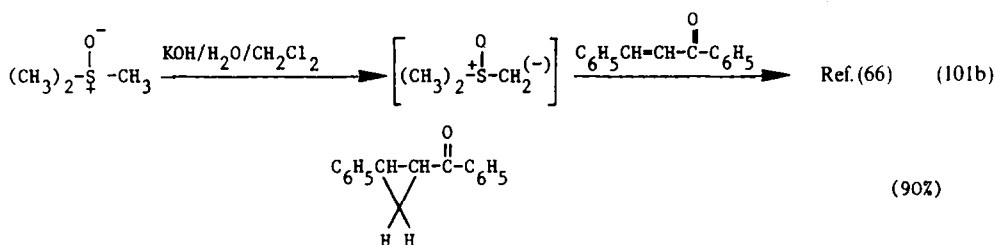
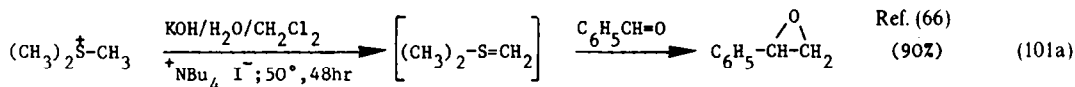
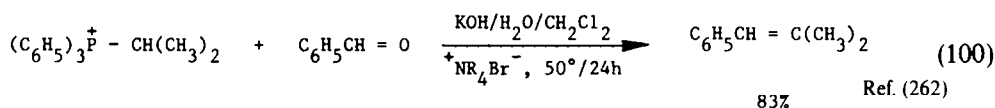



endo/exo (reaction temperature) : 3.2( $-115^\circ$ ); 1.9( $-105^\circ$ ); 0.11( $-80^\circ$ )

HMPT is one of the most valuable cosolvent for metallation purposes, it has the advantage over DMSO of not being easily metallated.<sup>260</sup> However, Corey<sup>42,62</sup> took advantage of this ability of DMSO to propose dimethyl salts in DMSO as valuable metallating agents. Dimethylformamide (DMF) is also a valuable solvent but is attacked by highly reactive carbanions producing aldehydes after hydrolysis. Protic solvents such as liquid ammonia, alcohols and water are used in case of moderately stabilized  $\alpha$ -heterosubstituted carbanions.

Particularly interesting are the phase transfer reactions<sup>81\*,82\*,83\*</sup> which occur in methylene chloride or benzene using KOH (50% in water) as base and tetraalkyl ammonium salts as catalysts. They allow the synthesis of olefins from phosphonium salts<sup>81b\*,262</sup> (Eq. 100), epoxides from sulfonium salts<sup>66,81b</sup> (Eq. 101), cyclopropanes from sulfoxonium salts<sup>66</sup> (Eq. 101) or chloroform<sup>81\*,83\*,84</sup> (Eq. 102) and carbonyl compounds from an acyl anions equivalent<sup>122</sup> (Eq. 27).

Interestingly the same transformations required before these finding strong basic media and anhydrous conditions.<sup>2\*, 7\*, 18\*, 21\*, 23\* - 25\*, 28\*</sup>

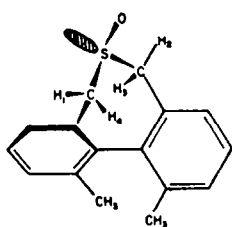


olefins :  $(\text{CH}_3)_2\text{C}=\text{CHCH}_3$  (60%) ;  $(\text{C}_4\text{H}_9\text{O})\text{HC}=\text{CH}_2$  (71%) ;  (72%)

Further interesting examples which disclose the crucial role of the solvent are mentioned below (Eq. 78): dimethylsulfide,<sup>218</sup> methyl phenyl sulfide<sup>208</sup> and isobutyl phenyl sulfide<sup>209</sup> are not metallated by n-BuLi in THF whereas addition of TMEDA in the first case,<sup>218</sup> DABCO in the second one<sup>208</sup> and t-BuLi in THF-HMPT in the third one<sup>209</sup> allows their quantitative metallation. The solvent effect proved to be very important in directing the reaction of alkylolithiums with selenides. Selenides are not easily metallated because strong base such as alkylolithiums needed for such purpose usually react on the selenium atom. Methyl phenyl selenide is cleaved by n-BuLi: in low yield in ether<sup>266</sup> and quantitatively in THF<sup>229</sup> but metallated in 45% yield in THF-TMEDA<sup>186b</sup> (Eq. 80a) (see Chapter IIB4). Methyl diphenyl phosphine behaves similarly<sup>267</sup> (see Chapter IIB4, Eq. 130). It was also found that n-BuLi does not react with vinyl phenyl selenide in pentane,<sup>136</sup> adds to its C-C bond in ether at 20°<sup>136, 231, 233</sup> (Eq. 80d) and cleaves the selenium-phenyl bond in THF at -78°<sup>136, 233</sup> (Eq. 81a). Use of LDA<sup>136</sup> or KDA<sup>109</sup> in THF leads to 1-metallo 1-phenylseleno ethylene (Eq. 81b) but phenyl selenolate is formed when THF-HMPT is used instead of THF<sup>136</sup> probably arising from  $\alpha$  or  $\beta$  elimination reactions. Phenylseleno acetals are recovered unchanged when reacted with n-BuLi, in pentane<sup>232</sup> even at 20° and easily cleaved in THF at -100°.<sup>186, 220, 221, 229</sup>

Only the two first members of the series, namely bis(phenylseleno)methane and ethane are cleaved by n-BuLi in ether<sup>232</sup> (at -78°C) and performing the reaction in the presence of HMPT (in THF or better in DME) lead to appreciable amounts of  $\alpha$ -lithio bis(phenylseleno)alkanes<sup>107</sup> especially with the two first members of the series. Finally, the crucial role of the solvent for the stereoselective metallation of sulfoxides was in several instances noticed<sup>199, 268, 269</sup> and this is exemplified in Eq. (103).<sup>268</sup>



Relative rate of exchange  
of  $\alpha$  protons

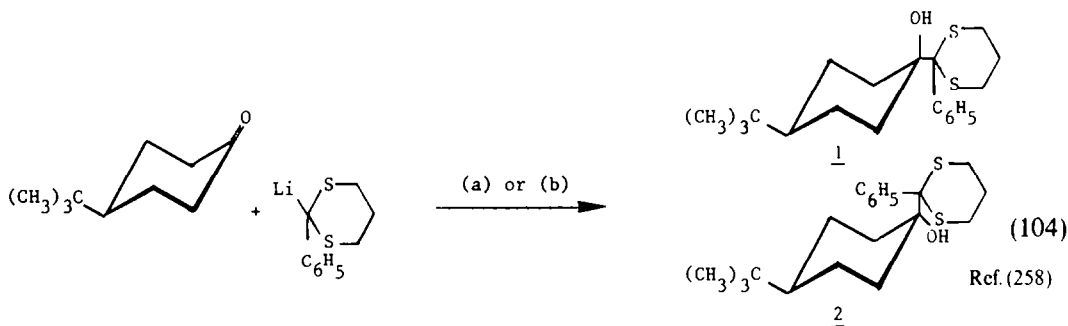
Solvent Base	Results
t-BuOD t-BuOK	$H_1/H_2 = 1/1100$ $H_3/H_4 = 1/4$
CD <sub>3</sub> OD CD <sub>3</sub> ONa	$H_1/H_2 = 1/200$ $H_3/H_4 = 250/1$

Ref. (268)

(103)

(b) *Role of the solvent for carbanion reactions.* The solvent has a very high implication for  $\alpha$ -heterosubstituted organometallics reaction and numerous examples are described in this field in the literature.

- Basic solvents (i.e. HMPT) sometimes needed for the generation of the carbanion, favor the enolisation of carbonyl compounds on further reaction<sup>258</sup> (Eq. 98).
- the direction of attack of carbanion to rigid cyclanones is highly dependant on the nature of the solvent and is exemplified<sup>258</sup> in Eq. (104);



- (a) cyclohexane 25°, 2hr  $\frac{1}{2}$  74/16  
 (b) THF -20°, 2hr; 25°, 1.5hr  $\frac{1}{2}$  75/00

Ref. (258)

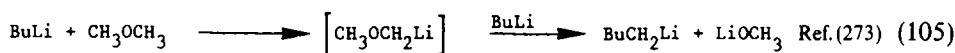
- the stereochemistry of the olefins prepared by the Wittig reaction is directly related to the polarity of the solvent used<sup>20\*,41,42,62,271</sup> which is thought to allow or not the reversibility of the betaine (Eq. 4);
- the solvent has also a crucial role in directing the reaction of heterosubstituted organometallics to enones either directly on the C<sub>1</sub> or C<sub>3</sub> site under kinetic control or via equilibration under thermodynamic control. This will be discussed in more detail in Chapter 1B.

#### IA6 Stability of $\alpha$ -heterosubstituted organometallics

$\alpha$ -heterosubstituted organometallics are sometimes unstable and are transformed in several different ways. As usual these side reactions are highly dependant on the nature of the groups directly attached on the carbanionic center, inter alia on the nature of the heteroatomic moiety, and on the experimental conditions used.

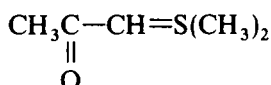
##### (a) Decomposition reactions.

Halogeno carbanions<sup>33\*,34\*,38\*-40\*,272</sup> and sulfonium<sup>9\*,28\*</sup> ylides are the most prone to  $\alpha$ -elimination reactions.  $\alpha$ -elimination reaction was also described<sup>260</sup> for  $\alpha$ -lithio HMPT (-30°, 1-3 days half-lives > 50%). Half-lives of diphenylsulfonium ethylide, allylide and cyclopropylide appear to be 0.1 hr (20°), 0.5 hr (-15°) and 0.05 hr (25°) respectively (Ref. 28\*, p. 23). Methoxy methyl lithium<sup>273</sup> (Eq. 105) lithio nitrosamines,<sup>11\*</sup> methylselenomethyl lithium<sup>232</sup> (ether 20°, 1 hr), triphenylplumbyl methyl lithium<sup>274</sup> (THF, 20°, 2 hr, 17% recovery), triphenyl stannyl methyl lithium<sup>274</sup> (THF, 20°, 2 hr: 20% recovery) are unstable.



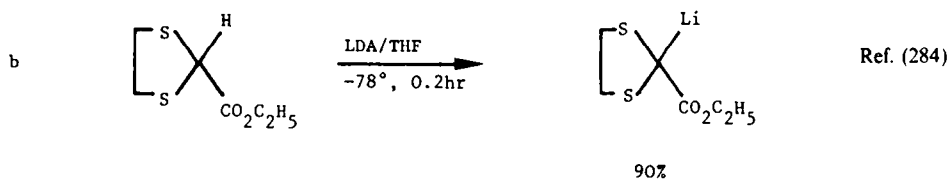
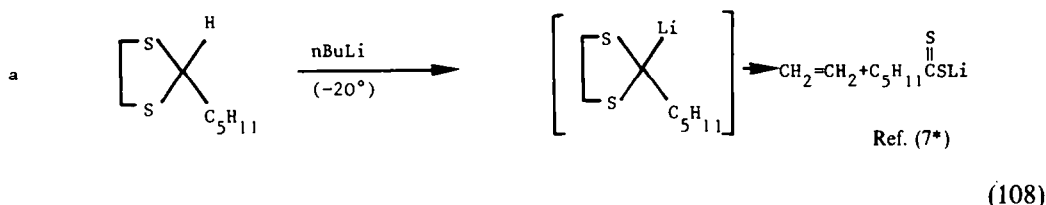
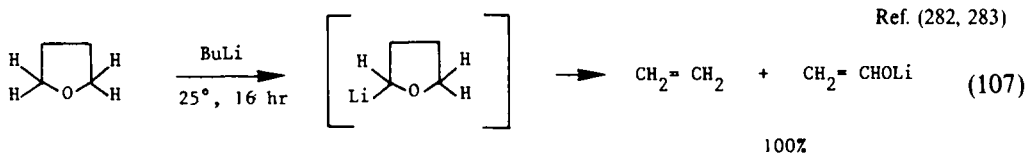
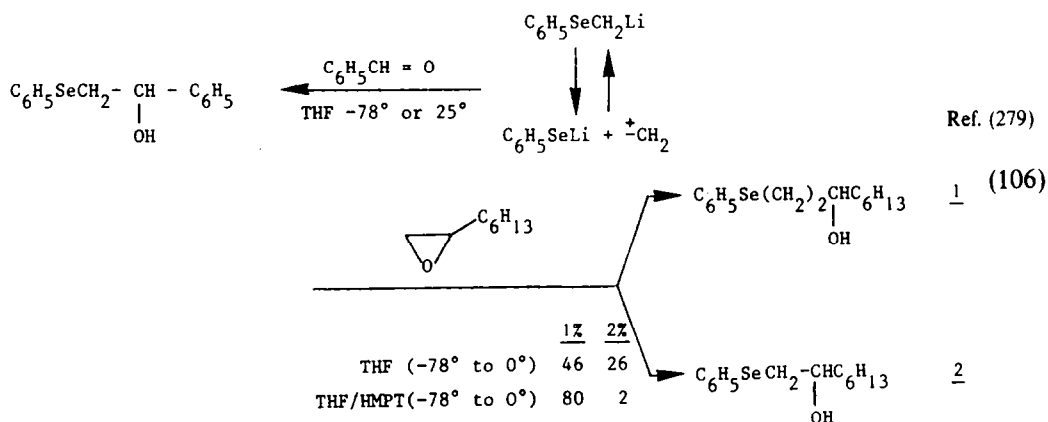
On the other hand methylthiomethylithium<sup>218</sup> (in hexane/TMEDA, 20°, 4 hr), phenylthiomethylithium<sup>208</sup> (THF/DABCO, 0°, 1 hr), trimethylsilylmethylithium<sup>14\*, 15\*, 275-276</sup> (pentane/TMEDA, 25°, 96 hr), diphenylphosphorylmethylithium<sup>187</sup> (pentane; 29°, 120 hr), phenylselenomethylithium<sup>186b</sup> (THF, 25°, 15 hr), phenyltelluromethylithium<sup>274, 278</sup> (THF, 0°, 24 hr), diphenylarsanyl methylithium<sup>274</sup> (THF, 20°, 2 hr - 100% recovery), diphenyl stibanylithium<sup>274</sup> (THF, 20°, 2 hr - 80% recovery) and phosphorus ylides<sup>18\*-22\*</sup> are quite stable at 20° even for quite long periods of time. Organometallics in which the carbanionic center is an sp<sup>2</sup> carbon or in which the carbanionic center is part of a cyclopropyl ring (cf (Eq. (84))<sup>33\*, 237</sup> and Table VIIB, entry r and u) are less prone to decomposition than the corresponding sp<sup>3</sup> carbanion with the exception of diphenylsulfonium cyclopropylide.<sup>28\*, 167</sup>

The more stabilized the carbanionic center is the less the carbanion is prone to decomposition [(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>S=CHC<sub>2</sub>H<sub>5</sub> half life 20°, 0.1 hr but



can be distilled bp<sub>0.8</sub>: 135 without decomposition (Ref. 33\*, p. 23)].

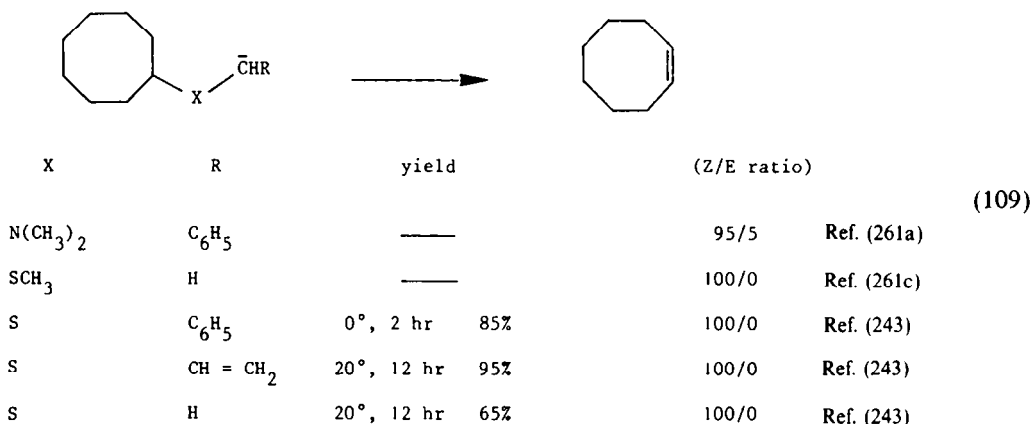
We have strong evidences<sup>279</sup> that α-selenomethylithiums in THF (even the phenylseleno one, which is stable till +20° and react quantitatively with carbonyl compounds at +20° are in equilibrium with the selenolate and probably the corresponding carbene. α-Selenomethylithiums produce both the expected 3-hydroxy-1-selenononane and the unexpected 2-hydroxy-1-selenooctane on reaction with 1,2-oxidooctene (Eq. 106). We found that this last reaction can be prevented by addition of HMPT to the medium.



Similar observations have been disclosed in the case of tris(phenylthio)<sup>467</sup> tris(alkylthio)<sup>280</sup> and tris(phenylseleno)<sup>186</sup> -methylolithiums.

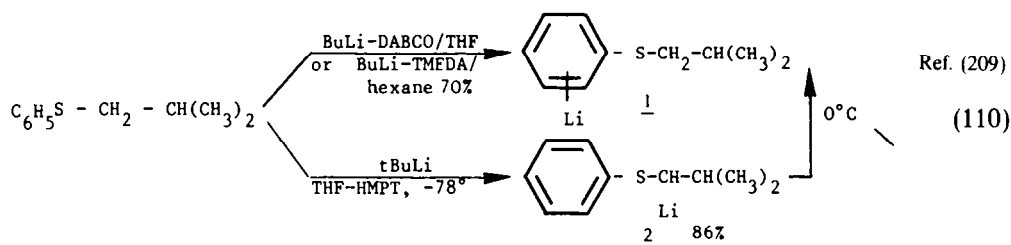
( $\beta$ ) Some carbanions decompose via a  $\beta$  elimination or a fragmentation process. This is the case of  $\alpha$ -lithio tetrahydrofuran<sup>282, 283</sup> (Eq. 107) and  $\alpha$ -lithiodithioacetal in which the two sulfur atoms are part of 5-membered cycle<sup>7\*</sup> (Eq. 108a). In the last case the decomposition is prevented by increasing the carbanion stabilization for example by addition of an extra carbomethoxy group<sup>284</sup> (Eq. 108b).

( $\gamma$ ) Others decompose via an  $\alpha'\beta$  elimination. This reaction close to the aminoxide (Cope reaction) sulfoxide and selenoxide elimination, was observed with ammonium salt,<sup>9\*, 261a, b</sup> sulfonium salts<sup>9\*, 392, 509</sup> (Eq. 109). We recently found<sup>509</sup> that selenonium salts produce olefins presumably via ylide formation and  $\alpha'\beta$  elimination ((see Chapter IIIC3b, Eq. 176, 177)) and Biellmann found<sup>243</sup> that similar reaction occurs when THF or benzene solutions of alkylthiomethylolithium, alkylthiobenzylolithium and alkylthioallyllithiums stand for prolonged period (15 hr) at room temperature.<sup>243</sup>



(b) In several instances the carbanion isomerized.

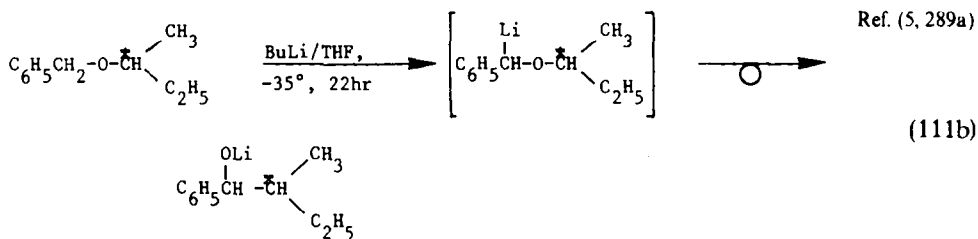
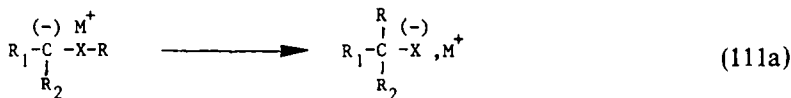
This is sometimes the case when the heteroatom is directly linked to a phenyl group. Anisole,<sup>285</sup> thioanisole,<sup>208, 286</sup> diphenyl methyl phosphine<sup>206</sup> seem to be metallated kinetically in the aromatic ring; in case of thioanisole it has been shown<sup>286</sup> that the first ring metallated derivative further isomerizes to produce phenylthiomethylolithium. In the case of isobutyl phenylsulfide however the kinetic metallation (t-BuLi/THF/HMPT) occurs on the alkyl chain<sup>209</sup> at -78° (Eq. 110) but the resulting carbanion isomerizes producing the ring metallated derivative when the temperature rises to 0°.



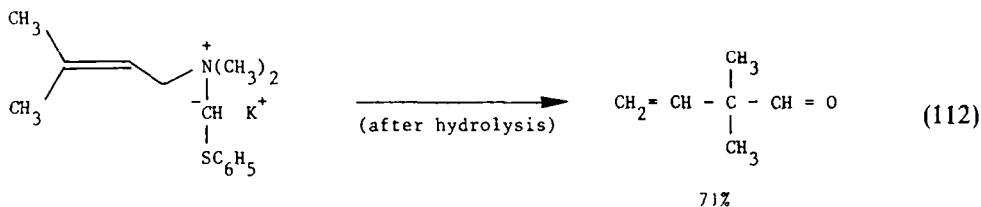
Phenylselenoalkyllithiums behave similarly: phenylselenomethylolithium is stable for prolonged period of time at 0° in THF<sup>186b</sup> or in ether<sup>232</sup> whereas some mono alkyl homologues are stable at -78° for several hours (10 hr) but isomerise to the more stable ring metallated derivative when stirred in ether for 1-2 hr at 20° (Eq. 148, Chapter III).

(c) In other cases the group attached to the heteroatom migrates onto the carbanionic center (Eq. 111a). The migrating group (R, Eq. 111a) may be an alkyl, allyl or aryl group, the carbanionic center usually bears an allyl, benzyl or phenacyl group and such rearrangement occurs in ethers<sup>5\*, 289</sup> [Wittig rearrangement (Eq. 111b)], in ammonium<sup>5\*, 287, 295\*</sup> (Stevens rearrangement) and sulfonium salts.<sup>5\*</sup>

In (lithio benzyl)alkyl esters the migration tendency of alkyl groups increases in the order: methyl, ethyl, isopropyl, tert-butyl ( $k_{rel}$ : 1:40:162:2080)<sup>288</sup> and in case of optically active 2-butyl benzyl ether

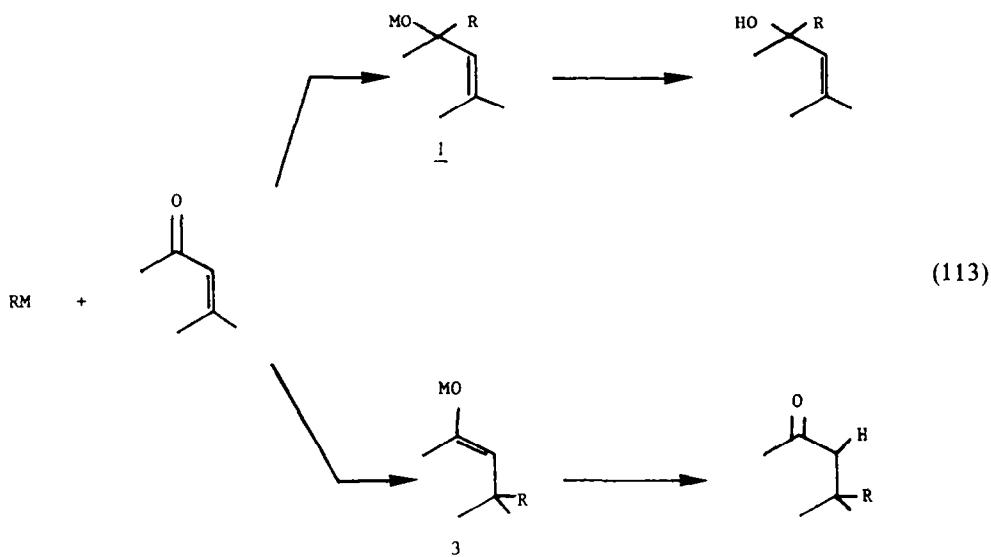


(Eq. 111), the sec butyl group migrates with 60% retention of its configuration.<sup>289</sup> Allyl migration is often accompanied by displacement of the double bond whatever the product is an ether<sup>297</sup> (Eq. 112), a sulfide,<sup>290, 291</sup> a sulfonium ylide<sup>292, 293</sup> or an ammonium salt<sup>264, 294, 295\*</sup> (Eq. 112). Finally the migration of an alcyryl group producing an allenic alcohol was also described.<sup>297</sup>



#### IB C<sub>1</sub> VERSUS C<sub>3</sub> REACTIVITY OF $\alpha$ -HETEROSUBSTITUTED ORGANOMETALLICS WITH ENONES

$\alpha$ -Enones have ambident reactivity toward nucleophiles and can lead either to an alcoholate **1** by C<sub>1</sub> attack or to an enolate **3** by C<sub>3</sub> addition (Eq. 113).



A large variety of  $\alpha$ -heterosubstituted organometallics, mainly organolithiums have been reacted with  $\alpha$ -enones and as expected all the possibilities from the pure C<sub>1</sub> or C<sub>3</sub> adduct to a mixture of the two, have been uncountered depending on the nature of the reactants. Till recently it was not possible to explain and above all to forecast experimental results. However some recently published theoretical work and pertinent experimental observations are beginning to clarify the situation. Furthermore, it is now possible in several instances to direct selectively C<sub>1</sub> or C<sub>3</sub> the reaction, of a specific  $\alpha$ -heterosubstituted organometallic.

Our purpose was to collect (Tables I-V) a large variety of results already described in the literature which involve  $\alpha$ -heterosubstituted organometallics and to discuss some of these examples.

The nature of the formed product(s) and the ratio of the  $C_1$  and  $C_3$  adducts is dependant on:

*The nature of the organometallic*

- (a) the nature of the carbon bearing the charge ( $sp^3$  or  $sp^2$ )
- (b) the number and the nature of the substituents branched on the carbanionic center
- (c) the nature of the cationic counterpart.

*The nature of the electrophilic partner*

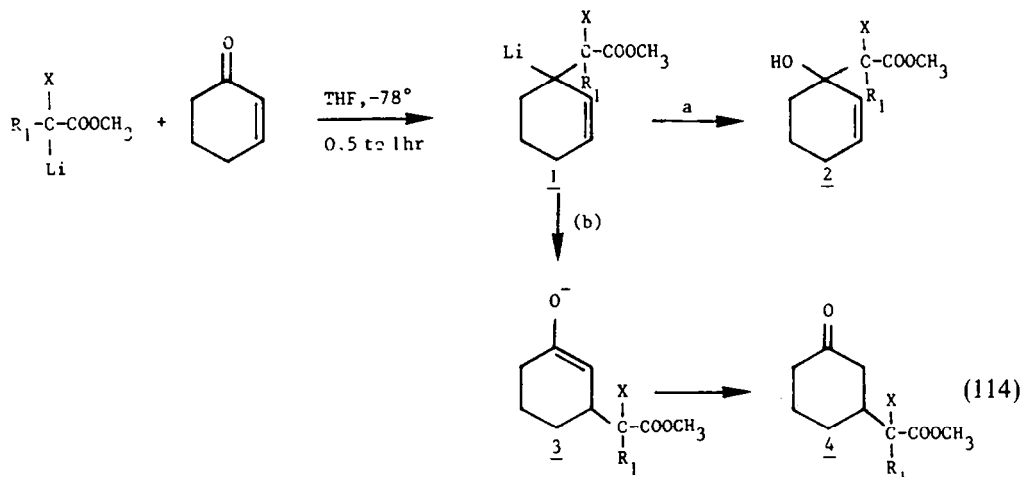
*The experimental conditions used*

- (a) the nature of the solvent
- (b) the temperature under which the reaction is performed.

IB1 In many cases the reactions are reversible<sup>244, 304, 307, 314, 315, 327; (a) 301\*, 329, 330</sup>

(see for example Table II, 5D-6D; 21D-36D; Table IVa, 3D, 4D).

In solvents of low polarity usually the  $C_1$  attack occurs first leading to the alcoholate  $1^b$  which produces after equilibration the enolate  $3$ .<sup>c, 244, 307, 314, 315</sup> This equilibration which is observed with carbanions quite well stabilized or/and delocalized (high HOMO),<sup>326, 331, 332</sup> is achieved by raising the temperature,<sup>d, 244, 307, 314, 315</sup> by increasing the polarity of the medium<sup>307, 315</sup> (sometimes by addition of HMPT,<sup>e, 315, 329</sup>) or by conjugation of both effects<sup>f, 315</sup> (Eq. 114).



X	R <sub>1</sub>	a)	b)	yield in: 2(%) and 4(%)	Ref.
C <sub>6</sub> H <sub>5</sub> O	CH <sub>3</sub>	H <sub>2</sub> O, -78°		88      8	Ref. (244)
		-78 to 25°; H <sub>2</sub> O		0      84	Ref. (244)
C <sub>6</sub> H <sub>5</sub> Se	H	H <sub>2</sub> O, -78°		68      3	Ref. (315)
		-78 to 25°, H <sub>2</sub> O		3      68	Ref. (315)
		HMPT, -45°, 4.5hr; H <sub>2</sub> O, -45°		3      68	Ref. (315)

This equilibration can formally occurs in a cage of solvent or via two completely independant moieties. Proofs in favor of one of the two processes lack presently although efforts have been spent in this field.<sup>330, 256</sup> The major problem in search of the intimate mechanism arise from the isomerisation at the  $C_1$  site, ( $C_1 \rightleftharpoons C_1$ ) which can occur at the same time as the  $C_1 \rightarrow C_3$  isomerisation.

We in fact found in case of the alcoholates  $C_{1a}$  and  $C_{1b}$  from cyclohexenone and  $\alpha$ -lithio  $\alpha$ -phenylselenoacetate that one of the two stereoisomers  $C_{1a}$  transforms to the other  $C_{1b}$  in THF at the temperature where each  $C_{1a}$  and  $C_{1b}$  produces the corresponding  $C_3$  adduct.<sup>256</sup>

Equilibration can also occur in the  $C_3$  adduct. This is the case of chalcone and  $\alpha$ -lithio phenylselenoacetate<sup>256</sup> (Eq. 115). The initial ratio of the two stereoisomers of  $3$  change a little by

<sup>a</sup> The starting alcoholate was not prepared<sup>301, 329</sup> from the same  $\alpha$ -heterosubstituted carbanion.

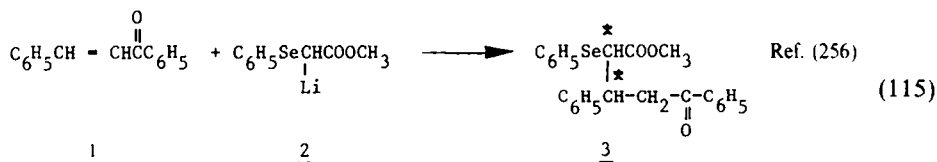
<sup>b</sup> Table II 21D, 24D, 27D, 28D; Table IV 1A, 3C, 5C, 7D, 17G, 21G, 22G; Table IV 37D.

<sup>c</sup> Table II 23D, 26D, 29D, 32D; Table IV 2A, 4C, 6C, 8D (eq. 114).

<sup>d</sup> Compare Table IV 4C to 3C; 6C to 5C; 8D to 7D; Table IV 38D to 37D.

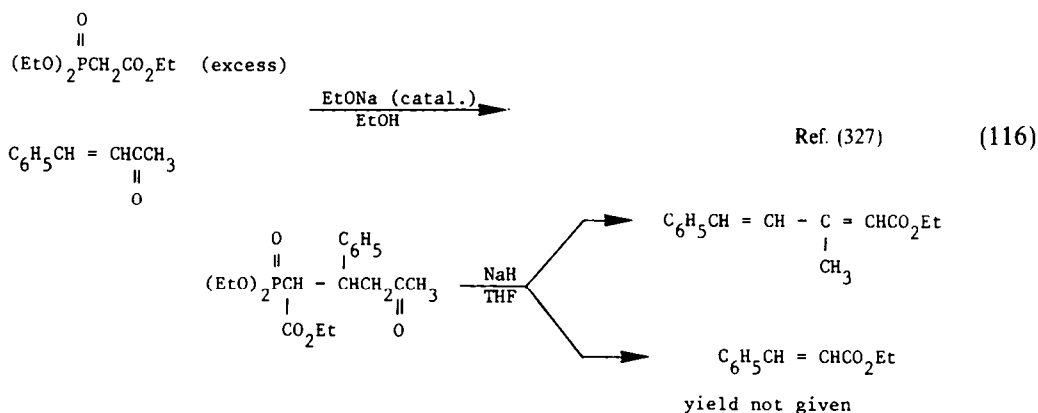
<sup>e</sup> Compare Table IV 19G to 18C, 23G to 22G.

<sup>f</sup> Compare Table IV 20G to 19G or 18G, 24G to 23G or 22G.



raising the temperature ( $-78$  to  $25^\circ$ ) or by addition of HMPT (to the THF solution) prior to raising the temperature to  $-45^\circ$ .

Finally the  $\text{C}_3 \rightarrow \text{C}_1$  equilibration was once described and found not to occur in a cage of solvent<sup>327</sup> (trapping of the "carbanionic" species with benzaldehyde) (Eq. 116).



**IB2** In other cases the reactions are not reversible<sup>s, 219, 304-306, 330, 536\*</sup>

Once the adduct is formed it cannot be transformed to the other one by the methods just presented (Eq. 117, 118a).

(a) It was recently simultaneously found by Brown,<sup>306</sup> Seyden Penne<sup>219</sup> and ourselves,<sup>219, 304</sup> that the nature of the solvent *used before* the addition of the enone to some carbanions has a crucial effect in directing<sup>h</sup> the addition either at  $\text{C}_1$  or at  $\text{C}_3$ . The more polar solvent usually favours the  $\text{C}_3$  attack<sup>h, 219, 304, 306</sup> under kinetic control. Similar tendency is found in the case of 1-lithio 1,1-bis(methylseleno) ethane when kryptant is added to the medium prior to the addition of cyclohexenone<sup>304</sup> (Eq. 117 a<sub>3</sub>).

Finally, we recently observed<sup>256, 536a, b</sup> that 1,1-bis(methylseleno) 1-lithio ethane and its thioanalogue preponderantly adds  $\text{C}_3$  to 2-hexenal ( $\text{C}_3/\text{C}_1$ : 45/18) in THF/HMPT whereas others acyl anion equivalents such as 2-lithio-2-methyl-1,3-dithiane<sup>536</sup> reacts at random  $\text{C}_3$  and  $\text{C}_1$  ( $\text{C}_3/\text{C}_1$ : 24/33) and 1,1-bis(phenylthio)-1-lithio ethane adds selectively  $\text{C}_1$  ( $\text{C}_3/\text{C}_1$ : 6/27) with the same aldehyde under similar conditions. Interestingly all these organometallics add specifically  $\text{C}_1$  to the same enone when reacted in THF.<sup>256, 536a, b</sup>

(b) In case of some SS acetal S oxides both the  $\text{C}_1$  and the  $\text{C}_3$  adducts are simultaneously formed,<sup>i, 311</sup> each one does not revert when the temperature is raised but the  $\text{C}_1/\text{C}_3$  ratio was found very dependant on the temperature at which the enone is added to the medium and surprisingly the higher  $\text{C}_1/\text{C}_3$  ratio is observed when the reaction is performed at high temperature<sup>i, 311</sup> (for different results, see Ref. 312, 313).

**IB3** Finally in several instances it is not yet possible to assess if the products obtained are formed directly or after equilibration<sup>j, 25\*, 65, 219, 244, 284</sup> (Eq. 115, 118b).

Many of these observations were only very recently disclosed and not yet widely applied.

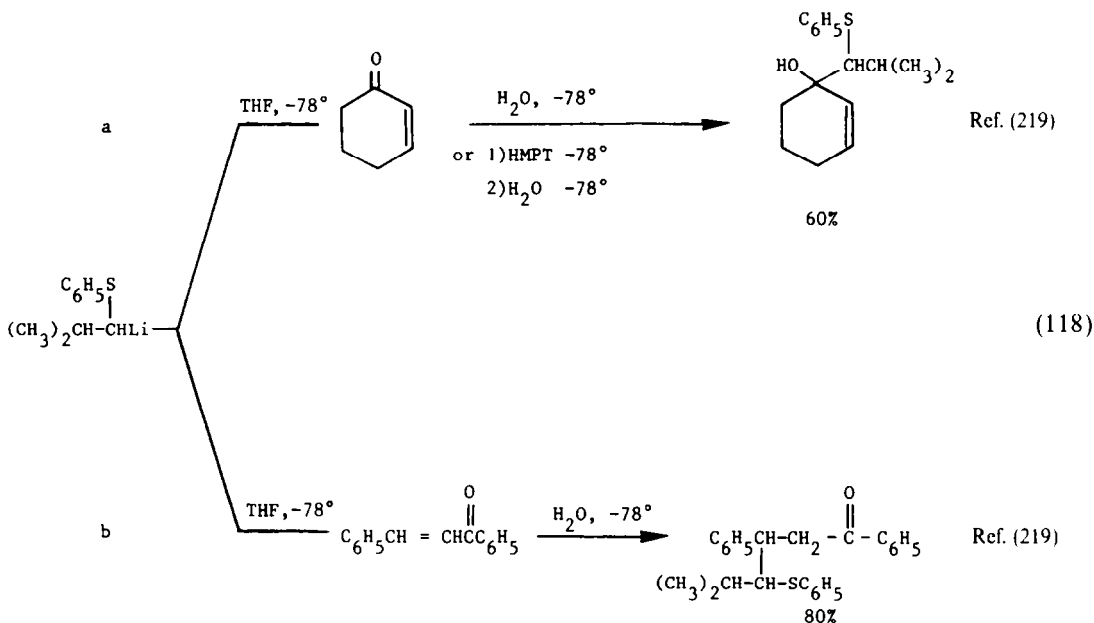
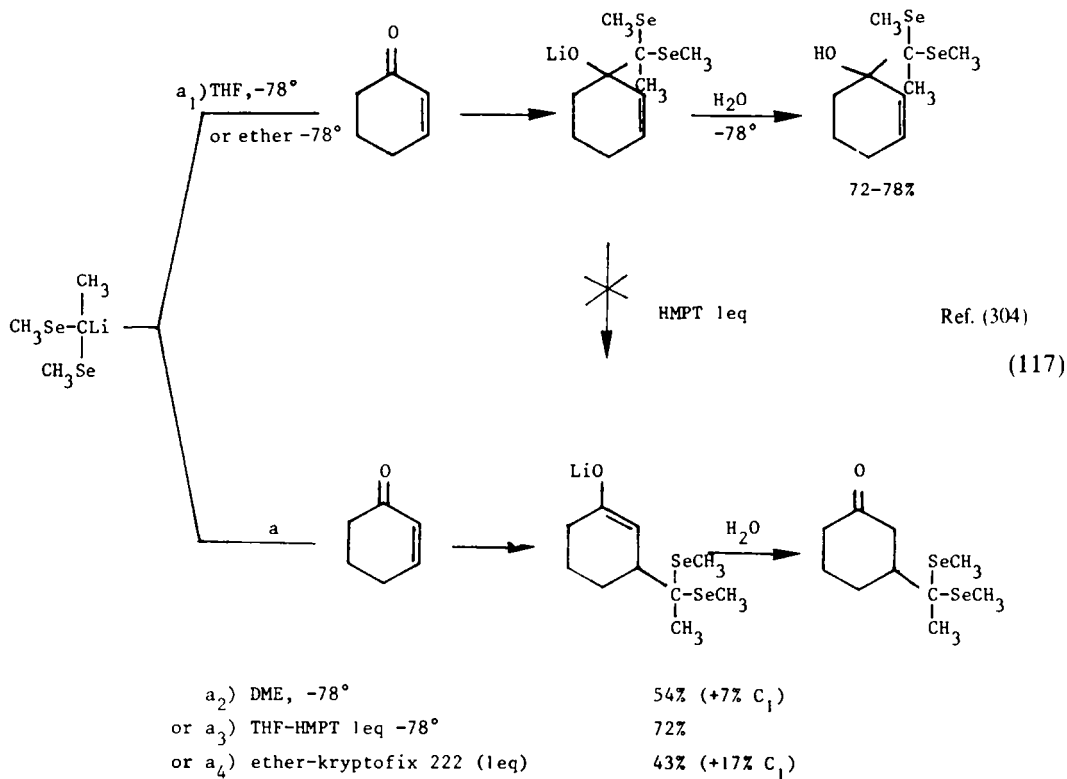
The following generalizations on the reactivity of  $\alpha$ -heterosubstituted organometallics with  $\alpha$ -enones can be tentatively done but care must be taken when attempting such generalization if subsequent reactions which make one pathway irreversible can occur (Tables I-V).

\* Table I 1B, 2B, 5D-9D, 15G-24G, Table II 1D-3D, 9D, 11D, 13D, 15D, 17D, 19D, 45D, 47D, 48D, 51G, 55G; Table III; Table IV 27B, 28B; Table IV 35A, 36A.

<sup>h</sup> Compare for example Table I 10D to 8D; Table II 10D to 9D, 12D to 11D, 14D to 13D, 16D to 15D, 18D to 17D, 20D to 19D, 46D to 45D, 49G to 48G, 52G, 53G and 56G, 57G to 51G, 55G (eqn 117).

<sup>i</sup> Compare Table III 9D to 8D. Compare also Table III 5D to 4D.<sup>311</sup>

<sup>j</sup> Table I 12D; Table IV 9A, 33G; Table IV 40D, 41D.



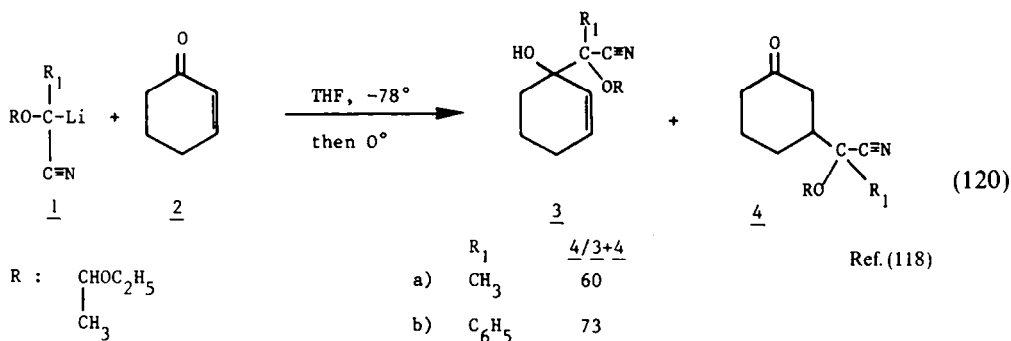
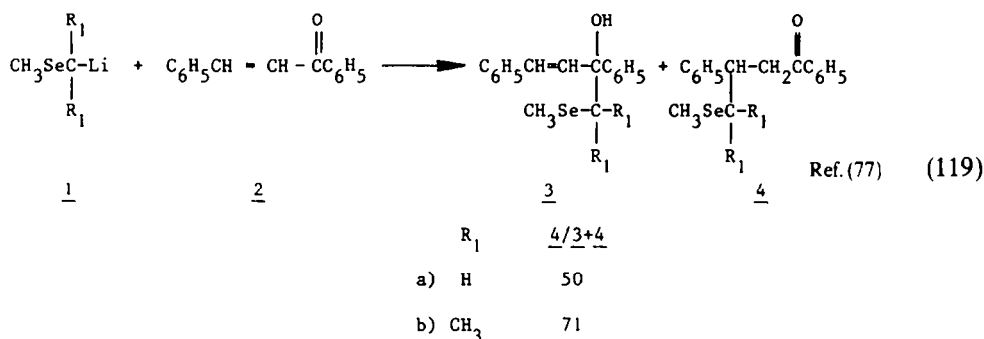
**IB4** All other things being equal the carbanion the more substituted<sup>k, 62, 65, 77, 304, 308, 317</sup> (Eq. 119) or bearing the bulkier group<sup>l, m, 118, 308</sup> (Eq. 120) usually lead to higher percentage of the C<sub>3</sub> adduct.

This can be due to steric and/or electronic repulsions both at the level of the reagents and/or in the C<sub>1</sub> adduct which allow in the latter case the reaction to revert. Alternatively one can also propose a stepwise electron transfer which leads to a radical particularly favourable on the more substituted carbon atom.

<sup>k</sup> Compare Table I 22G to 16G; Table II 6D or 5D to 3D; Table II 37D, 38D to 1D, 2D. For similar observation in non heterosubstituted alkylolithiums, see Ref. 339. Be careful in comparing Table V 10E, 11E, 12E to 2E; 22D, 23D to 18D.

<sup>l</sup> Compare Table IV 30A to 27A; Table II 37D, 38D to 1D, 2D.

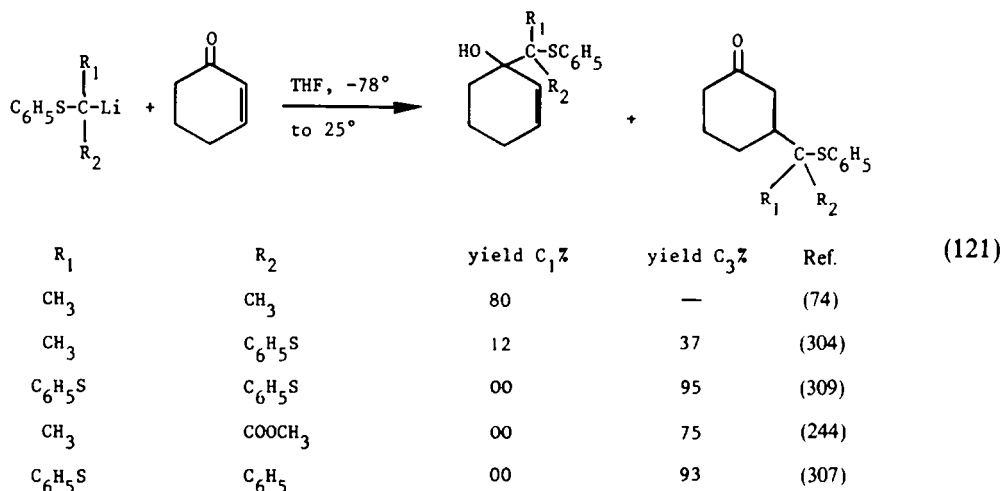
<sup>m</sup> Compare Table V 14E to 16E; Table IV 4C to 27C: The nitrile group is smaller than an ester group, an ester has a lower acidifying effect than a nitrile but better delocalizes an  $\alpha$ -carbanion.<sup>331</sup>



IB5 The highest stabilized or delocalized (the softest)<sup>334</sup> carbanion lead to preferential formation of the C<sub>3</sub> adduct<sup>n, 25\*, 118, 244, 284, 308, 309, 314, 315</sup> kinetically<sup>n</sup> or under equilibrating<sup>c-f</sup> conditions (Eqs. 114, 120).

All things being equal, a higher percentage of C<sub>3</sub> adduct is observed:

- when the heteroatom attached to the carbanionic center is changed by another one which is thought to better stabilize it.<sup>o, 244, 315, 118, 316, 335</sup>
- when the other group attached to the heteroatom better delocalized the carbanion “through the heteroatom”.<sup>p, 219, 244, 308</sup>
- by adjunction of a carbanion stabilizing group<sup>q, 52, 77, 118, 219, 244, 304, 307, 316, 321, 335</sup> (Eq. 121). The better delocalization of the charge on the ester group compared to the nitrile group was proposed to explain the higher tendency of α-phosphino esters to react C<sub>3</sub>.<sup>m, 318, 331</sup>



<sup>n</sup> Table II 41D–44D; Table II 37D–38D; Table II 39D, 40D; Table IV 40D–43D.

<sup>o</sup> However in case of α-lithio selenoesters<sup>332</sup> the C<sub>1</sub> adduct to cyclohexanone which isomerizes to the C<sub>3</sub> by raising the temperature or on standing after addition of HMPT is generally obtained at –78° whatever the solvent used (THF or THF-HMPT) (1 eqn). These results have to be compared to the highly solvent dependant kinetic C<sub>1</sub> or C<sub>3</sub> adduct formation in case of α-lithio selenoacetals<sup>304</sup> with the same enone.

<sup>q</sup> Compare Table IV 9D to 18G and 5C; 33G to 30A; Table IV 37D, 38D to 35A, 36A.

<sup>p</sup> Compare Table II 3D to 1D; Table IV 9D to 7D; 18G to 17G.



**IB6** The cation has also a great influence in directing  $C_1$  or  $C_3$  the attack of the organometallic to  $\alpha$ -enones<sup>332</sup>

It interacts either with the nucleophilic reagent (ionic association) or with the enone (C=O) complexation).<sup>332</sup> Quite no systematic studies have been performed in this field with carbanions bearing different cations. As expected  $\alpha$ -heterosubstituted cuprates (soft metals)<sup>336\*</sup> lead to higher percentage of the  $C_3$  adduct<sup>r.127, 251, 252, 314</sup> (Eq. 92) than the corresponding lithium salt (hard metal)<sup>336\*</sup> mainly used. But the synthesis of organocopper is not a simple task since in many instances copper promoted dimerisation of  $\alpha$ -heterosubstituted organometallics prevent their further use<sup>238, 254, 255, 256</sup> (Eqs. 94, 95, 96).

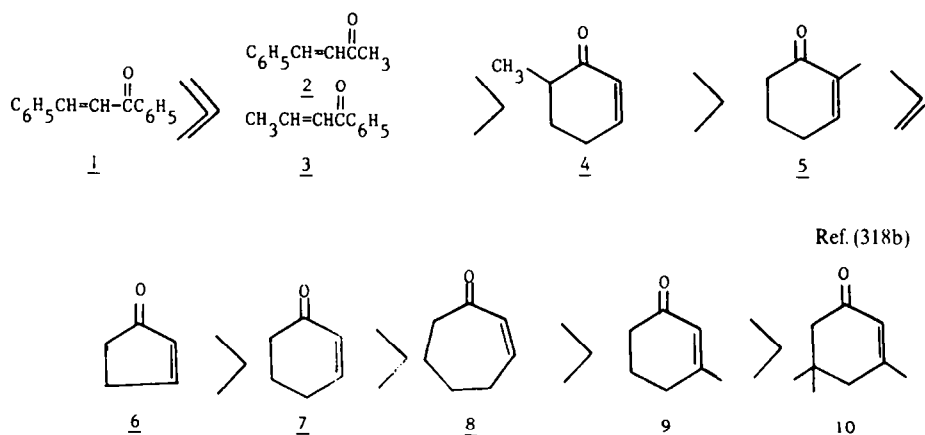
**IB7** Both electronic and steric factors on the enones greatly influence the ratio of  $C_1/C_3$  adduct formed from a specific  $\alpha$ -heterosubstituted organometallics

— Chalcone has, among the various enones generally described, the highest tendency to produce the  $C_3$  adduct<sup>s, 11\*, 77, 219, 232, 318, 326</sup> (even probably by direct attack on the C site). This aptitude can be explained by the particularly low energy level of its LUMO.<sup>318</sup>

Methylene triphenyl phosphorane,<sup>96, 317</sup> methylene dimethylsulfurane,<sup>62</sup> methylene dimethylselenurane<sup>68</sup> and ethylidene triphenyl phosphorane<sup>317</sup> are the rare examples of exclusive formation of the  $C_1$  adduct<sup>t</sup> with chalcone. This aptitude to react more at  $C_3$  has been in several instances noticed for enones flanked by a phenyl group on the  $C_3$  or the  $C_1$  carbons.<sup>318</sup> Dypnone (3-methyl-chalcone) which bears a methyl substituent at  $C_3$ , reacts sluggishly and does not lead to the  $C_3$  adduct. This result was explained in terms of steric hindrance around the  $C_3$  site.<sup>318</sup>

— Steric reasons have been also invoked to explain the highest percentage of  $C_1$  adduct usually obtained with aldehydes (see Tables I–V), the higher  $C_3/C_1$  ratio observed with ketones bearing bulky groups around the carbonyl group<sup>u, 118</sup> and the lower  $C_3/C_1$  ratio disclosed when the  $C_3$  site is uncumbered.<sup>v, 65, 118, 309</sup> The higher propensity of well stabilized carboethoxy methylene dimethyl sulfurane to react  $C_3$  even with crotonaldehyde (but not with  $\beta, \beta$ -dimethylacroleine)<sup>317</sup> and the selectivity with which  $\alpha$ -lithio unsaturated  $\alpha$ -alkoxynitriles<sup>118</sup> and  $\alpha$ -lithio  $\alpha$ -thiophenyl acetate<sup>314</sup> react  $C_3$  with 3-methyl cyclohexenone contrast with the just disclosed generalization.

We have presented in eqn (122) several ketones tentatively classified by their decreasing aptitude to react  $C_3$  with organometallics. The series  $1 \gg 2 \equiv 3 > 7 > 9 > 10$  follow the decreasing aptitude of these enones to react  $C_3$  with  $\alpha$ -lithio phenyl acetonitrile in THF–HMPT (80–20) and interestingly this order parallels the order of the half wave potential of their electrolytic reduction<sup>337</sup> and the classification of their LUMO orbitals.<sup>244, 318, 338</sup>



\* Compare Table II DE to Table I 8D; Table II 31D, 28D, 25D to 15D; Table II 55G to Table I 21G; Table IV 31A to 27A.

<sup>r</sup> compare Table IV 16D to 15D; the results described in Ref. 251 with those recently described which show a high tendency to such lithio derivatives to react  $C_3$  with enones Table II 4D, 5D.<sup>304</sup>

<sup>s</sup> Compare Table I 2B to 1B, 12D to 8D; 16G to 15G, 22G to 23G. Be careful in comparing Table V 10E, 11E, 12E to 8E; 13E to 14E, 15E to 16E.

<sup>t</sup> Be careful in comparing Table V 1E, 2E to 10E, 11E, 12E; see Table V 20D, 37G. See Table V 20D, 37D. See also Ref. 304.

<sup>u</sup> Compare Table IV 29A to 27A.

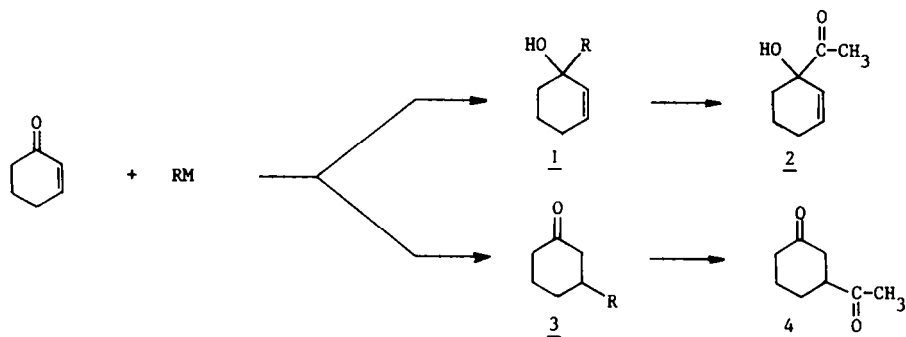
<sup>v</sup> Compare Table II 44D to 42D; Table IV 28A to 27A, Table V 24D to 22D.

### IB8 Proposed mechanism

Hypotheses concerning the formation of the C<sub>3</sub> adduct involve<sup>307</sup> the delivering of the two electrons at once or a stepwise electron transfert. There is no support for one of this proposal but probably both possibilities will be found depending on the nature of the two partners.

### IB9 Tentative prediction of experimental results

It is too early to propose a means to foreseen with complete confidence the reactivity of an  $\alpha$ -heterosubstituted alkyl lithium with a specific  $\alpha$ -enone. It can be suggested that the C<sub>1</sub> adduct



RM	conditions	1%	3%	2%*	4%*	Ref.
	THF, -33° to 20°, 18hr	66	00			(305)
	THF-HMPT (1eq), -78°	05	65			(304)
$(C_6H_5S)_2C \begin{matrix} \diagup CH_3 \\ \diagdown Li \end{matrix}$	THF, -78° ; H <sub>2</sub> O, -78°	11	22			(304)
	THF-HMPT (1eq)	02	41			(304)
$(C_6H_5Se)_2C \begin{matrix} \diagup CH_3 \\ \diagdown K \end{matrix}$	THF, -78°	76	00			(109)
$(CH_3Se)_2C \begin{matrix} \diagup CH_3 \\ \diagdown Li \end{matrix}$	Ether, -78°	78	<2	56		(304)
	THF-HMPT (1eq), -78°	<2	72		56	(304)
$C_2H_5O-CH-O-C \begin{matrix} \diagup CH_3 \\ \diagdown Li \\   \\ CH_3 \\   \\ CN \end{matrix}$	THF/HMPT, -78° to 0°	60	40			(118)
	THF, -65°*	100	00			(127)
	R:CH <sub>3</sub> THF/(CH <sub>3</sub> ) <sub>2</sub> S, -40° to 10°	00	66		53	(127)
	R:C <sub>2</sub> H <sub>5</sub> THF	00	84			(252)
	THF, -78 to -10°, 1h		90		<54	(322)
$CH_3-C(=O)-Ni$	Ether, -50°, 12h				34	(328)

\* Even with CuI but in the absence of (CH<sub>3</sub>)<sub>2</sub>S the C<sub>1</sub> adduct is the only one observed.

\* Refers to overall yield from cyclohexenone

Table I.

Entry	Organometallic			Enone	Starting conditions	Final conditions	Isolated yield $\frac{C_3}{C_1+C_2}$	$\frac{C_3}{C_1+C_2}$	Ref.
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>						
1B	CH <sub>3</sub> N-NO	H	H	Li cyclohexenone	THF/Hexane 8/2 -80° (5-10hr)	H <sub>2</sub> O	75/02	3	[11 <sup>a</sup> ]
2B	CH <sub>3</sub> N-NO	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	THF/Hexane 8/2 -80° (5-10hr)	H <sub>2</sub> O	45/55	55	11 <sup>a</sup>
3B	NO <sub>2</sub>	H	C <sub>2</sub> H <sub>5</sub>	HN(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	not stated		00/75	100	139 b
4B	NO <sub>2</sub>	H	C <sub>2</sub> H <sub>5</sub> C(CH <sub>3</sub> ) <sub>2</sub> HN(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	not stated	not stated		00/83	100	139 b
5D	C <sub>6</sub> H <sub>5</sub> S	H	H	Li C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	not stated		largely	C <sub>1</sub>	301
6D	C <sub>6</sub> H <sub>5</sub> S	H	CH <sub>3</sub>	Li cyclohexenone	THF, -78°, 2hr	H <sub>2</sub> O	85/00	0	74
7D	C <sub>6</sub> H <sub>5</sub> S	H	CH <sub>3</sub>	Li cyclohexenone	THF/HMPPT(2.5eq), -78°, 2hr	H <sub>2</sub> O, -78°	5/30	8 <sup>b</sup>	74
8D	C <sub>6</sub> H <sub>5</sub> S	H	CH(CH <sub>3</sub> ) <sub>2</sub>	Li cyclohexenone	THF, -78°, 2hr	H <sub>2</sub> O, -78°	60/00	0	219
9D	C <sub>6</sub> H <sub>5</sub> S	H	CH(CH <sub>3</sub> ) <sub>2</sub>	Li cyclohexenone	THF, -78°, 2hr	HMPPT(2.5eq)-78°, 2hr; H <sub>2</sub> O, -78°	60/00	0	219
10D	C <sub>6</sub> H <sub>5</sub> S	H	CH(CH <sub>3</sub> ) <sub>2</sub>	Li cyclohexenone	THF/HMPPT(2.5eq)-78°, 2hr	H <sub>2</sub> O, -78°	00/56	100	[209]
11D	C <sub>6</sub> H <sub>5</sub> S	H	CH(CH <sub>3</sub> ) <sub>2</sub>	Li 2-methyl cyclopentenone	THF/HMPPT(2.5eq)-78°	H <sub>2</sub> O	00/57	100	209
12D	C <sub>6</sub> H <sub>5</sub> S	H	CH(CH <sub>3</sub> ) <sub>2</sub>	Li C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	THF, -78°, 2hr	H <sub>2</sub> O, -78°	00/80	100	[302]
13D	C <sub>6</sub> H <sub>5</sub> S	H	CH <sub>2</sub>	Li cyclohexenone	THF, 0°, 0.5hr	H <sub>2</sub> O, 0°	85/00	0	[303]
14D	C <sub>6</sub> H <sub>5</sub> S	H	CH <sub>2</sub>	Li CH <sub>3</sub> CH=C(C=O)CH <sub>3</sub>	THF, 0°, 0.5hr	H <sub>2</sub> O, 0°	96/00	0	[303]
15G	CH <sub>3</sub> Se	H	H	Li C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O, 20°	87/00	0	77
16G	CH <sub>3</sub> Se	H	H	Li C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O, 20°	35/35	50	77
17G	CH <sub>3</sub> Se	H	CH <sub>3</sub>	Li C <sub>6</sub> H <sub>5</sub> CH=CH-CHO	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O, 20°	90/00	0	77
18G	CH <sub>3</sub> Se	H	C <sub>6</sub> H <sub>13</sub>	Li CH <sub>3</sub> CH=CH(C=O)CH <sub>3</sub>	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O, 20°	65/00	0	77
19G	CH <sub>3</sub> Se	H	C <sub>6</sub> H <sub>13</sub>	Li cyclohexenone	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O, 20°		0	232
20G	CH <sub>3</sub> Se	CH <sub>3</sub>	CH <sub>3</sub>	Li cyclohexenone	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O, 20°	65	0	232
21G	CH <sub>3</sub> Se	CH <sub>3</sub>	CH <sub>3</sub>	Li cyclohexenone	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O, 20°	55/00	0	77
22G	CH <sub>3</sub> Se	CH <sub>3</sub>	CH <sub>3</sub>	Li C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O, 20°	21/47	70	77
23G	C <sub>6</sub> H <sub>5</sub> Se	CH <sub>3</sub>	CH <sub>3</sub>	Li cyclohexenone	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O	63/00	0	77
24G	CH <sub>3</sub> Se	CH <sub>2</sub>	CH <sub>2</sub>	Li cyclohexenone	THF, -78°, 1hr	-78° to 20°, H <sub>2</sub> O	88/00	0	232

A, B, C, D, E, F and G refer to organometallic bearing respectively carbon atom(s) (A), nitrogen atom(s) (B), oxygen atom(s) (C), sulfur atom(s) (D), phosphorus atom(s) (E), chlorine atom(s) (F) and selenium atom(s) (G).

Table II.

Entry	Organometallic			Enone	Starting conditions	Final conditions	Isolated Yield $\frac{C_3}{C_1+C_3} \%$	Ref.
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>					
1D	CH <sub>3</sub> S	CH <sub>3</sub> S	H	Li cyclohexenone	THF, -78°		84/00 00	308
2D	CH <sub>3</sub> S	CH <sub>3</sub> S	n-C <sub>3</sub> H <sub>7</sub>	Li cyclohexenone	THF, -78°		68/00 00	308
3D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	H	Li cyclohexenone	THF, -78°, 0.2hr	H <sub>2</sub> O, -78° or HMPT(-78 to 20°)H <sub>3</sub> O <sup>+</sup>	—/— 55	304
4D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	H	Li cyclohexenone	THF-HMPT(1eq), -78°, 0.2hr	H <sub>2</sub> O, -78°	05/65 92	804
5D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	CH <sub>3</sub>	Li cyclohexenone	THF, -78°, 0.2hr	H <sub>2</sub> O, -78°	—/— 75	304
6D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	CH <sub>3</sub>	Li cyclohexenone	THF, -78°, 0.2hr	HMPT, -78° to 20°, 1hr; H <sub>3</sub> O <sup>+</sup> , 20°	02/41 93	304
7D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	CH <sub>3</sub>	Li cyclohexenone	THF-HMPT(1eq), -78°, 0.2hr	H <sub>2</sub> O, -78°	01/41 97	304
8D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	CH <sub>3</sub>	Li carvone	THF-HMPT(1eq), -78°, 0.2hr	H <sub>2</sub> O, -78°	01/63 99	304
9D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	H	Li cyclohexenone	THF, -78°, 0.2hr	H <sub>2</sub> O, -78° or HMPT(-78 to 20°)H <sub>3</sub> O <sup>+</sup>	80/00 00	304
10D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	H	Li cyclohexenone	THF-HMPT(1eq), -78°, 0.2hr	H <sub>2</sub> O, -78°	06/70 92	306
11D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	H	Li cycloheptenone	THF, -78°	aqNH <sub>4</sub> Cl, -78°	—/— 1	306
12D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	H	Li cyclopentenone	THF-HMPT(2eq), -78°	aqNH <sub>4</sub> Cl, -78°	—/— 74	306
13D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	H	Li cyclopentenone	THF, -78°	aqNH <sub>4</sub> Cl, -78°	—/— 98	306
14D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	H	Li cyclopentenone	THF-HMPT(2eq), -78°	aqNH <sub>4</sub> Cl, -78°	—/— 98	306
15D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>3</sub>	Li cyclohexenone	THF, -78°, 0.2hr	H <sub>2</sub> O, -78° or HMPT(-78 to 20°)H <sub>3</sub> O <sup>+</sup>	66/00 00	304
16D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>3</sub>	Li cyclohexenone	THF-HMPT(1eq), -78°, 0.2hr	H <sub>2</sub> O, -78°	05/65 92	304
17D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>3</sub>	Li carvone	THF, -78°, 0.2hr	H <sub>2</sub> O, -78°	—/— 00	304
18D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>3</sub>	Li carvone	THF-HMPT(1eq), -78°, 0.2hr	H <sub>2</sub> O, -78°	05/65 92	304
19D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>13</sub>	Li cyclohexenone	THF, -78°, 0.2hr	H <sub>3</sub> O <sup>+</sup> , -78° or HMPT(-78 to 20°)H <sub>3</sub> O <sup>+</sup>	—/— 00	304
20D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>13</sub>	Li cyclohexenone	THF-HMPT(1eq), -78°, 0.2hr	H <sub>3</sub> O <sup>+</sup> , -78°	07/60 90	304
21D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>5</sub>	Li cyclopentenone	Hexane-THF (1.8:1)-78°	H <sub>2</sub> O, -78°	—/— 6	307
22D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>5</sub>	Li cyclopentenone	THF, -78°	H <sub>2</sub> O, -78°	—/— 50	307
23D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>5</sub>	Li cyclopentenone	THF, -78° then 25°, 1hr	H <sub>2</sub> O, +25°	00/81 100	307
24D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>5</sub>	Li cyclohexenone	Hexane-THF (1.8:1)-78°	H <sub>2</sub> O, -78°	—/— 5	307
25D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>5</sub>	Li cyclohexenone	THF, -78°	H <sub>2</sub> O, -78°	—/— 35	307
26D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>5</sub>	Li cyclohexenone	THF, -78° then 25°, 1hr	H <sub>2</sub> O, +25°	00/93 100	307
27D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> S	CH <sub>2</sub> -CH <sub>2</sub> S	C <sub>6</sub> H <sub>5</sub>	Li cycloheptenone	Hexane-THF (1.8:1)-78°	H <sub>2</sub> O, -78°	100/00 0	307

28D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -S	C <sub>6</sub> H <sub>5</sub>	Li	cycloheptenone	THF, -78°	H <sub>2</sub> O, -78°	90/10	10	307
29D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -S	C <sub>6</sub> H <sub>5</sub>	Li	cycloheptenone	THF, -78° then 25°, 1hr	H <sub>2</sub> O, +25°	00/86	100	307
30D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -S	C <sub>6</sub> H <sub>5</sub>	Li	2-methyl cyclohexenone	Hexane-THF (1.8:1)-78°	H <sub>2</sub> O, -78°	-/-	33	307
31D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -S	C <sub>6</sub> H <sub>5</sub>	Li	2-methyl cyclohexenone	THF, -78°	H <sub>2</sub> O, -78°	-/-	95	307
32D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -S	C <sub>6</sub> H <sub>5</sub>	Li	2-methyl cyclohexenone	THF, -78° then 25°, 1hr	H <sub>2</sub> O, +25°	00/93	100	307
33D				cyclohexenone	THF, -78° then 25°, 1hr	H <sub>2</sub> O, +25°	00/90	100	307
34D				CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	THF, -78° then 25°, 1hr	H <sub>2</sub> O, +25°	00/34	100	307
35D				C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	THF, -78° then 25°, 1hr	H <sub>2</sub> O, +25°	00/60	100	307
36D				cyclohexenone	THF, -78° then 25°, 1hr	H <sub>2</sub> O, +25°	00/96	100	307
37D	CH <sub>3</sub> S	Si(CH <sub>3</sub> ) <sub>3</sub>	Li	cyclopentenone	THF, -78°, 2hr; 20°, 5hr	H <sub>2</sub> O	00/73	100	308
38D	CH <sub>3</sub> S	Si(CH <sub>3</sub> ) <sub>3</sub>	Li	cyclohexenone	THF, -78°, 2hr; 20°, 5hr	H <sub>2</sub> O	00/78	100	308
39D	CH <sub>3</sub> S	Sn(CH <sub>3</sub> ) <sub>3</sub>	Li	cyclohexenone	THF, -78°, 2hr; 20°, 5hr	H <sub>2</sub> O	00/81	100	308
40D	CH <sub>3</sub> S	Sn(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub>	Li	cyclohexenone	THF, -78°, 2hr; 20°, 5hr	H <sub>2</sub> O	00/79	100	308
41D	CH <sub>3</sub> S	CH <sub>3</sub> S	Li	cyclohexenone	THF, 20°, 12hr	H <sub>2</sub> O, 20°	-/-	50	308
42D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	Li	cyclohexenone	THF, -78°	H <sub>3</sub> O <sup>+</sup>	00/95	100	309
43D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	Li	2-methyl cyclohexenone	THF, -78°	H <sub>3</sub> O <sup>+</sup>	00/85	100	309
44D	C <sub>6</sub> H <sub>5</sub> S	C <sub>6</sub> H <sub>5</sub> S	Li	3-methyl cyclohexenone	THF, -78°	H <sub>3</sub> O <sup>+</sup>	00/05	100	309
45D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -S	Si(CH <sub>3</sub> ) <sub>3</sub>	Li	cyclohexenone	THF, -78° to 20°, 4hr	H <sub>2</sub> O	80/00	0	310
46D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -S	Si(CH <sub>3</sub> ) <sub>3</sub>	Li	cyclohexenone	THF-HMP(2eq), -78°	aq NH <sub>4</sub> Cl	-/-	95	306
47D	SCH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -S	Si(CH <sub>3</sub> ) <sub>3</sub>	Li	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	THF, -78°	H <sub>2</sub> O	66/00	0	310
48G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	THF, -78°, 0.2hr	H <sub>2</sub> O, -78°	68/06	8	232
49G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	THF-HMP(1eq), -78°, 0.2hr	H <sub>2</sub> O, -78°	03/75	96	232
50G	C <sub>6</sub> H <sub>5</sub> Se	C <sub>6</sub> H <sub>5</sub> Se	K	cyclohexenone	THF, tBuOK -78°	H <sub>2</sub> O	76/00	00	109
51G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	ether, -78°, 2.5hr	H <sub>2</sub> O, -78°	78/02	2.5	304
52G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	ether-HMP(0.5eq), -78°, 2.5hr	H <sub>2</sub> O, -78°	55/19	25	304
53G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	ether-HMP(1eq), -78°, 2.5hr	H <sub>2</sub> O, -78°	04/60	94	304
54C	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	ether kryptofix 222(1eq)-78°, 2.5hr	H <sub>2</sub> O, -78°	17/43	71	304
55G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	THF, -78°, 2.5hr	H <sub>3</sub> O <sup>+</sup> , -78° or HMP(-78° to 20°)H <sub>2</sub> O <sup>+</sup>	43/16	29	304
56G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	THF-HMP(1eq), -78°, 2.5hr	H <sub>2</sub> O, -78°	01/72	99	304
57G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	cyclohexenone	DME, -78°, 2.5hr	H <sub>2</sub> O, -78°	01/54	67	304
58G	CH <sub>3</sub> Se	CH <sub>3</sub> Se	Li	carvone	THF-HMP(1eq)-78°, 0.2hr	H <sub>2</sub> O, -78°	05/66	92	304

Table III.

Entry	Organometallic			Enone	Starting conditions	Final conditions	Isolated yield $\frac{C_3}{C_1+C_3}\%$	Ref.	
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>						M
1D	CH <sub>3</sub> S	CH <sub>3</sub> SO	H	Li	2-benzyl cyclopentenone	THF, -78°	49/19	29	311
2D	CH <sub>3</sub> S	CH <sub>3</sub> SO	H	Li	cyclohexenone	THF, -78°	66/07	9	311
3D	CH <sub>3</sub> S	CH <sub>3</sub> SO	H	Li	4 i-propyl cyclohexenone	THF, -78°	85/00	00	311
4D	CH <sub>3</sub> S	CH <sub>3</sub> SO	H	Li	cyclopentenone	THF, -78°, 6hr	22/57	76	311
5D	CH <sub>3</sub> S	CH <sub>3</sub> SO	H	Li	cyclopentenone	THF, 0°, 3hr	25/41	66	311
6D	(CH <sub>3</sub> ) <sub>2</sub> CHS	(CH <sub>3</sub> ) <sub>2</sub> CHSO	H	Li	cyclopentenone	THF, -78°	79/14	13	311
7D	pTolyl S	pTolyl SO	H	Li	cyclopentenone	THF, -78°	79/07	6	311
8D	CH <sub>3</sub> S	CH <sub>3</sub> SO	CH <sub>3</sub>	Li	cyclopentenone	THF, -78° or THF	28/61	68	311
9D	CH <sub>3</sub> S	CH <sub>3</sub> SO	CH <sub>3</sub>	Li	cyclopentenone	THF, 0°, 3hr	—/—	28	311
10D	C <sub>2</sub> H <sub>5</sub> S	C <sub>2</sub> H <sub>5</sub> SO	C <sub>2</sub> H <sub>5</sub>	Li	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	THF, -20°, 2hr	00/96	100	312
11D	C <sub>2</sub> H <sub>5</sub> S	C <sub>2</sub> H <sub>5</sub> SO	C <sub>2</sub> H <sub>5</sub>	Li	cyclopentenone	THF, -20°, 2hr	00/70	100	312
12D	C <sub>2</sub> H <sub>5</sub> S	C <sub>2</sub> H <sub>5</sub> SO	C <sub>6</sub> H <sub>13</sub>	Li	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	not stated	00/90	100	313
13D	C <sub>2</sub> H <sub>5</sub> S	C <sub>2</sub> H <sub>5</sub> SO	(CH <sub>2</sub> ) <sub>2</sub> CFC-(C <sub>2</sub> H <sub>5</sub> ) <sub>5</sub>	Li	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	not stated	00/96	100	313

Table IV.

Entry	Organometallic			Enone	Starting conditions	Final conditions	Isolated yield $\frac{C_3}{C_1+C_2+C_3}$	R.F.	
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>						
1A	CH <sub>3</sub>	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	H <sub>3</sub> O <sup>+</sup> , -78°	88/05	5	2:4
2A	CH <sub>3</sub>	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	THF, -78°	07/83	92	2:4
3C	CH <sub>3</sub> O	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	THF, -78°	75/12	13	2:4
4C	CH <sub>3</sub> O	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	THF, -78°	05/62	92	2:4
5C	C <sub>6</sub> H <sub>5</sub> O	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	H <sub>3</sub> O <sup>+</sup> , -78°	88/08	10	2:4
6C	C <sub>6</sub> H <sub>5</sub> O	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	-78° to 25°; H <sub>3</sub> O <sup>+</sup> , 25°	00/84	100	2:4
7D	CH <sub>3</sub> S	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	H <sub>3</sub> O <sup>+</sup> , -78°	63/07	10	2:4
8D	CH <sub>3</sub> S	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	THF, -78°	00/85	100	2:4
9D	C <sub>6</sub> H <sub>5</sub> S	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	THF, -78°	00/75	100	2:4
10D	C <sub>6</sub> H <sub>5</sub> S	CH <sub>3</sub>	COOCH <sub>3</sub>	Li	cyclohexenone	-78° to 25°; H <sub>3</sub> O <sup>+</sup> , 25°	00/86	100	2:4
11D	C <sub>6</sub> H <sub>5</sub> S	H	COOLi	Li	cyclohexenone	THF, -30°, 2hr	86/00	00	3:4
12D	C <sub>6</sub> H <sub>5</sub> S	H	COOCH <sub>3</sub>	Li	3-methyl cyclohexenone	THF, -60 to -10°, 6hr	30/83	100	3:4
13D	C <sub>6</sub> H <sub>5</sub> S	H	COOLi	Li	3-methyl cyclohexenone	THF, -50°, 2hr	72/00	00	3:4
14D	C <sub>6</sub> H <sub>5</sub> S	H	COOLi	Li	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	THF, -78°, 2.5hr	48/08	14	3:4
15D	C <sub>6</sub> H <sub>5</sub> S	H	COOCH <sub>3</sub>	Li	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	THF, -78°, 2hr	31/14	31	3:4
16D	C <sub>6</sub> H <sub>5</sub> S	H	COOCH <sub>3</sub>	Cu	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	THF, -78°	00/42	100	3:4
17G	CH <sub>3</sub> Se	H	COOCH <sub>3</sub>	Li	cyclohexenone	H <sub>3</sub> O <sup>+</sup> , -78°	54/03	5	3:5
18G	C <sub>6</sub> H <sub>5</sub> Se	H	COOCH <sub>3</sub>	Li	cyclohexenone	THF, -78°	47/17	28	3:5
19G	C <sub>6</sub> H <sub>5</sub> Se	H	COOCH <sub>3</sub>	Li	cyclohexenone	H <sub>2</sub> O, -78°	14/54	8	3:5
20G	C <sub>6</sub> H <sub>5</sub> Se	H	COOCH <sub>3</sub>	Li	cyclohexenone	H <sub>2</sub> O, -45°	03/70	93	3:5
21G	PCl <sub>5</sub> H <sub>4</sub> Se	H	COOCH <sub>3</sub>	Li	cyclohexenone	H <sub>3</sub> O <sup>+</sup> , -78°	50/05	6	3:5
22G	PCl <sub>5</sub> H <sub>4</sub> Se	H	COOtbu	Li	cyclohexenone	H <sub>3</sub> O <sup>+</sup> , -78°	73/02	4	3:5
23G	PCl <sub>5</sub> H <sub>4</sub> Se	H	COOtbu	Li	cyclohexenone	H <sub>2</sub> O, -78°	22/66	75	3:5
24G	PCl <sub>5</sub> H <sub>4</sub> Se	H	COOtbu	Li	cyclohexenone	H <sub>2</sub> O, -45°	03/52	95	3:5
25G	C <sub>6</sub> H <sub>5</sub> Se	H	COOCH <sub>3</sub>	Li	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	H <sub>2</sub> O, -78°	36/09	19	3:5
26G	C <sub>6</sub> H <sub>5</sub> Se	H	COOCH <sub>3</sub>	Li	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	THF-HMPPT, -78°, 6hr	07/37	85	3:5

TABLE IV (continued)

Entry	Organometallic			Enone	Starting conditions	Final conditions	Isolated		Ref.
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>				Yield C <sub>1</sub> %, C <sub>2</sub> %, C <sub>3</sub> %	C <sub>3</sub> C <sub>1</sub> +C <sub>2</sub> %	
27A	CH <sub>3</sub> (C <sub>2</sub> H <sub>5</sub> O) <sub>2</sub> HO	CH <sub>3</sub>	CN	cyclohexenone	THF-HMPT, -78°, 0.1hr	H <sub>2</sub> O, 0°	60	118	118
28A	"	CH <sub>3</sub>	CN	3-methyl cyclohexenone	THF-HMPT, -78°, 0.1hr	H <sub>2</sub> O, 0°	90/02	2	118
29A	"	CH <sub>3</sub>	CN	6-methyl cyclohexenone	THF-HMPT, -78°, 0.1hr	H <sub>2</sub> O, 0°	good yield	85	118
30A	"	C <sub>5</sub> H <sub>11</sub>	CN	cyclohexenone	THF-HMPT, -78°, 0.1hr	H <sub>2</sub> O, 0°	good yield	73	118
31A	"	CH <sub>2</sub> =CH	CN	cyclohexenone	THF-HMPT, -78°, 0.1hr	H <sub>2</sub> O, 0°	75	100	118
32A	"	CH <sub>3</sub> CH=CH	CN	cyclohexenone	THF-HMPT, -78°, 0.1hr	H <sub>2</sub> O, 0°	75	100	118
33G	C <sub>6</sub> H <sub>5</sub> Se	C <sub>6</sub> H <sub>13</sub>	CN	cyclohexenone	THF, -78°, 1hr	H <sub>2</sub> O, 0°	00/91	100	316
34B	C <sub>6</sub> H <sub>5</sub> CH=N	H	COOC <sub>2</sub> H <sub>5</sub>	cyclohexenone	THF, -78°	H <sub>2</sub> O, 0°	00/90	100	125
35A				cyclohexenone	THF, -78°	H <sub>2</sub> O/NH <sub>4</sub> Cl, -78°	82/00	0	244
36A				cyclohexenone	THF, +25°	H <sub>2</sub> O/NH <sub>4</sub> Cl	82/00	0	244
37D				cyclohexenone	THF, -78°	H <sub>2</sub> O/NH <sub>4</sub> Cl, -78°	C <sub>1</sub> /-	0(?)	244
38D				cyclohexenone	THF, +25°	H <sub>2</sub> O/NH <sub>4</sub> Cl	-/C <sub>3</sub>	100	244
39B				CH <sub>2</sub> = CH(C=O)CH <sub>3</sub>	NEt <sub>3</sub> /CH <sub>2</sub> Cl <sub>2</sub> , 20°	—	00/100	100	
40D	SCH <sub>2</sub> —	CH <sub>2</sub> S	COOCH <sub>3</sub>	3-chloro cyclohexenone	THF, -70°, 6hr	H <sub>2</sub> O	00/94	100	284a
41D	SCH <sub>2</sub> —	CH <sub>2</sub> —	COOCH <sub>3</sub>	cyclopentenone	THF, -78°, 1hr	H <sub>2</sub> O	00/93	100	25*
42D	C <sub>2</sub> H <sub>5</sub> S—	C <sub>2</sub> H <sub>5</sub> S	COOCH <sub>3</sub>	CH <sub>2</sub> = CH(C=O)—CH <sub>3</sub>	DME, 4°	H <sub>2</sub> O	00/93	100	284b
43D	C <sub>2</sub> H <sub>5</sub> S—	C <sub>2</sub> H <sub>5</sub> S	COOCH <sub>3</sub>	cyclohexenone	DME, 4°	H <sub>2</sub> O	00/97	100	284b

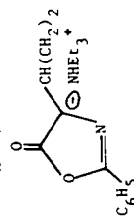
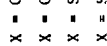
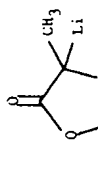




Table V.

Entry	Organometallic			Enone	Starting conditions	Final conditions	Isolated yield $\frac{C_3}{C_1+C_2+C_3}$	Ref.
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>					
1E	(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> P <sup>+</sup>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	THF, reflux	H <sub>2</sub> O, 20°	40	96
2E	"	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	THF, 0°	H <sub>2</sub> O, 20°	46 <sup>a</sup>	317
3E	"	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)mesityl	ether 0°, xylene 115°	H <sub>2</sub> O, 20°	00/41 <sup>b</sup>	96
4E	"	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	THF, -78°	H <sub>2</sub> O, 20°	88 <sup>a</sup>	317
5E	"	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	Li salt free	C <sub>6</sub> H <sub>6</sub> , 20°	32	317
6E	"	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	Li	THF, -20°	47	317
7E	"	H	COOCH <sub>3</sub>	CH <sub>3</sub> COOCH=CH(CO)C <sub>6</sub> H <sub>5</sub>	? not stated	H <sub>2</sub> O, 20°	00/92	100
8E	"	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	Li	THF, -78°	28 <sup>a</sup> /0	0
9E	"	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	Li	THF, 20°	7 <sup>a</sup> /3	30
10E	"	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	Li	THF, 20°	00/83 <sup>b</sup>	100
11E	"	CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub>	CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	Li	THF, 20°	00/77 <sup>b</sup>	100
12E	"	CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub>	CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	Li	THF, 20°	00/42	100
13E	(EtO) <sub>2</sub> PO	H	COOC <sub>2</sub> H <sub>5</sub> <sup>d</sup>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	K	H <sub>2</sub> O, 20°	2/90	98
14E	(EtO) <sub>2</sub> PO	H	COOC <sub>2</sub> H <sub>5</sub> <sup>d</sup>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	K	H <sub>2</sub> O, 20°	15/35	70
15E	(EtO) <sub>2</sub> PO	H	C <sup>n</sup> N <sup>d</sup> <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	K	H <sub>2</sub> O, 20°	05/70	93
16E	(EtO) <sub>2</sub> PO	H	C <sup>n</sup> N <sup>d</sup>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	K	H <sub>2</sub> O, 20°	55/30	65
17E	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> PO	H	C <sup>n</sup> N <sup>d</sup>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	K	H <sub>2</sub> O, 20°	02/40	95
18D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	H	cyclohexenone	? not stated	H <sub>2</sub> O, not stated	only <sup>c</sup>	62
19D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	H	carvone	DMSO/THF(1/1), 0° to 25°	H <sub>2</sub> O	89 <sup>c</sup> /00	00
20D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	DMSO/THF(1/1), 0° to 25°	H <sub>2</sub> O	87 <sup>c</sup> /00	00
21D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)H	DMSO, 0°	H <sub>2</sub> O	40 <sup>c</sup> /-	00
22D	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> S <sup>+</sup>	CH <sub>3</sub>	CH <sub>3</sub>	cyclohexenone	THF or DME, -60°, 1.5hr	H <sub>2</sub> O, not stated	00/74 <sup>b</sup>	100
23D	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> S <sup>+</sup>	CH <sub>3</sub>	CH <sub>3</sub>	2-methyl cyclohexenone	THF or DME, -70 to 30°, 3hr	H <sub>2</sub> O, not stated	00/86 <sup>b</sup>	100
24D	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> S <sup>+</sup>	CH <sub>3</sub>	CH <sub>3</sub>	3-methyl cyclohexenone	not stated	H <sub>2</sub> O, not stated	mainly <sup>c</sup>	00
25D	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> S <sup>+</sup>	CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub>	CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub>	carvone	DMSO, 0°	H <sub>2</sub> O	00/75 <sup>b</sup>	100
26D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	COOC <sub>2</sub> H <sub>5</sub>	cyclohexenone	Benzene, 80°, 18hr	H <sub>2</sub> O	00/71 <sup>b</sup>	100
27D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	COOC <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> =CH(C=O)CH <sub>3</sub>	CH <sub>3</sub> Cl <sub>2</sub> , 40°, 2.5hr	H <sub>2</sub> O	00/87 <sup>b</sup>	100
28D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	COOC <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>2</sub> C=CH(C=O)CH <sub>3</sub>	Benzene, 80°, 18hr	H <sub>2</sub> O	00/75 <sup>b</sup>	100
29D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	COOC <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> =C=CHO CH <sub>3</sub>	Benzene, 80°, 1hr	H <sub>2</sub> O	00/86 <sup>b</sup>	100

Entry	Organometallic			Enone	Starting conditions	Final conditions	Isolated yield $\frac{C_2}{C_1+C_3}$	Ref.
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>					
30D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	COOC <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub> -CH=CH-CHO	Acetone, 60°, 0.3hr	H <sub>2</sub> O	00/50 <sup>b</sup> 100	321
31D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	COOC <sub>2</sub> H <sub>5</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH=CH-CHO	Acetone, 60°	H <sub>2</sub> O	50 <sup>c</sup> /00 50	317
32D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	COONa	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	DMSO, 250°, 15 hr	H <sub>2</sub> O	00/59 <sup>b</sup> 100	124
33D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	H	cetone	DMSO, 0°	H <sub>2</sub> O	00/81 <sup>b</sup> 100	62
34D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	DMSO, 0°, 0.1hr; 25°, 2 hr; 50°, 1hr.	H <sub>2</sub> O	00/95 <sup>b</sup> 100	62
35D	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	NaOH/H <sub>2</sub> O, CH <sub>2</sub> Cl <sub>2</sub>	N(C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> I <sup>-</sup>	00/86 <sup>b</sup> 100	66
36D	p(CH <sub>3</sub> ) <sub>6</sub> H <sub>4</sub> SN <sup>+</sup> Me <sub>2</sub>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	DMSO, 25°	H <sub>2</sub> O	00/94 <sup>b</sup> 100	320
37D	C <sub>6</sub> H <sub>5</sub> SN <sup>+</sup> Me <sub>2</sub>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	THF, 25°, 4hr	H <sub>2</sub> O	00/100 <sup>b</sup> 100	323
38D	C <sub>6</sub> H <sub>5</sub> SN <sup>+</sup> Me <sub>2</sub>	CH <sub>2</sub>	CH <sub>2</sub>	(CH <sub>3</sub> ) <sub>2</sub> C=CH(C=O)CH <sub>3</sub>	DMSO, 25°, 20hr	H <sub>2</sub> O	00/61 <sup>b</sup> 100	324
39D	(CH <sub>3</sub> ) <sub>2</sub> CHSN <sup>+</sup> Me <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	DMSO, 25°, 12hr	H <sub>2</sub> O	00/86 <sup>b</sup> 100 <sup>b</sup>	325
40C	(CH <sub>3</sub> ) <sub>2</sub> Se <sup>+</sup>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)H	DMSO, 0°	H <sub>2</sub> O	71 <sup>c</sup> /00 00	68
41G	(CH <sub>3</sub> ) <sub>2</sub> Se <sup>+</sup>	H	H	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	DMSO, 0°	H <sub>2</sub> O	50 <sup>c</sup> /00 00	68
42 <sup>c</sup> Cl		H	COOCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	HMPT, 20°, 1 hr	H <sub>2</sub> O	60 <sup>c</sup> /00 00	326
43F Cl		C <sub>6</sub> H <sub>5</sub>	COOCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	HMPT/THF, -70°	H <sub>2</sub> O	- / - 100	326
44F Cl		C <sub>6</sub> H <sub>5</sub>	COOCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)C <sub>6</sub> H <sub>5</sub>	HMPT/THF, -70°	H <sub>2</sub> O	- / - 100 <sup>b</sup>	326
45F Cl		H	C≡N	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	HMPT, 20°, 1 hr	H <sub>2</sub> O	60 <sup>c</sup> /00 00	326
46F Cl		C <sub>6</sub> H <sub>5</sub>	C≡N	C <sub>6</sub> H <sub>5</sub> CH=CH(C=O)CH <sub>3</sub>	THF, -78°	H <sub>2</sub> O, -78°	- / - 100 <sup>b</sup>	326

<sup>a</sup> not isolated, a - olefin, b - cyclopropane, c - epoxide, d - 2 mole of phosphonate per mole of base used

formation should be exalted when the reaction is performed in the less polar solvent, at the lowest temperature and for the shortest time, whereas the  $C_3$  adduct should be favoured kinetically or thermodynamically when the reaction is performed in the more polar solvent at the highest temperature and during the longest time possible.‡

However whereas several results disclosed in this revue and also in general in the organometallic field<sup>256,339</sup> agree with these predictions, already some results described by Ogura<sup>311</sup> for  $\alpha$ -lithio S,S acetal S oxide are out of tune with them.

Equation (123) presents some comparative results already described for the introduction of acetyl anion equivalent at  $C_1$  or  $C_2$  of cyclohexanone.

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‡ This requires the absence of a side reaction which withdraws one of the intermediate.

## CHAPTER II

METHODOLOGY FOR  $\alpha$ -HETEROSUBSTITUTED ORGANOMETALLICS SYNTHESIS

The synthesis of an  $\alpha$ -heterosubstituted organometallic requires the choice of the right method which allows the introduction of the metal on the carbon bearing the heteroatom.

Several already well-established methods for the synthesis of organometallics<sup>1</sup> can be used for  $\alpha$ -heterosubstituted organometallics formation but rare are the ones which can be prepared by all the methods: that means that each method has quite drastic limitations. These limitations can be due to the instability of the organometallic at the temperature required for its synthesis or to the unavailability of the starting material.

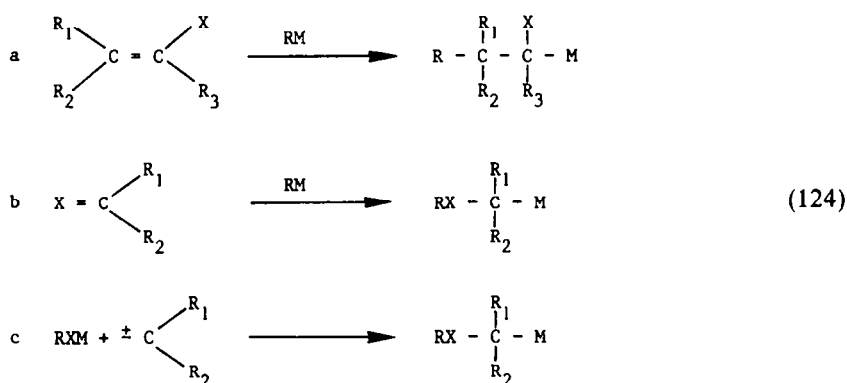
Because of the large number of carbanions of this kind known, we will restrict ourselves, in this chapter, to  $sp^3$  carbanions which bear *only one neutral heteroatom*, the other two substituents being exclusively *hydrogens or alkyl groups*. These organometallics are generally the less stabilized ones and thus the most difficult to prepare. In one instance (metallation reaction) for comparison purposes we have included some examples in which the heteroatom bears a partial or a full positive charge.

The  $\alpha$ -heterosubstituted carbanions (like other carbanions) can be prepared by addition (A) or substitution (B) reactions which are schematized below. This include:

(A1) addition reaction of organometallics onto  $\alpha$ -heterosubstituted olefins (Eq. 124a)

(A2) addition of an organometallic onto an heteroatom doubly linked to carbon atom (Eq. 124b)

(A3) additions of organometallics to carbenes (Eq. 124c).



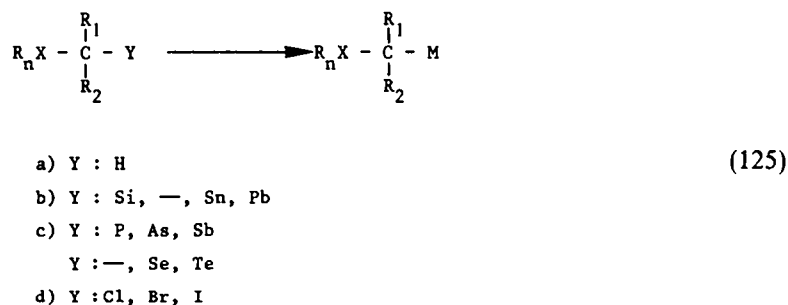
Substitution reactions which include:

(B1) the hydrogen metal-exchange (metallation) (Eq. 125a)

(B2) the halogen metal exchange (Eq. 125d)

(B3) the metal-metal exchange (transmetallation), the metal exchanged belonging to Group IVa in the Periodic Table (Eq. 125b).

(B4) the metalloide metal exchange in which the exchanged atom belongs to Groups Va and VIa and VIa in the Periodic Table (Eq. 125c).



All these classifications are of course formal since a continuum can be really found. For example, an enhanced metallic character is observed, whatever the group an atom belongs, if it belongs to a row of high value in the Periodic Table (Sn > Si; Sb > P; Te > S; I > Cl). However, one can pursue itself

that the heteroatom in silanes, germanes, stananes and plumbanes do not have electron lone pairs. Phosphines, arsines, stibines, sulfides, selenides and tellurides possess electron lone pairs and are nucleophilic. Whereas, alkylchlorides, bromides and iodides possess electron lone pairs but are not nucleophilic.

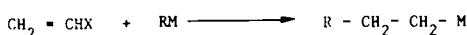
We will discuss more specifically the metalloide metal-exchange and the use of  $\alpha$ -selenocarbanions in organic synthesis. However, we will briefly present the different methods (Eqs. 124, 125) for  $\alpha$ -heterosubstituted carbanions synthesis. We don't have the claim to be exhaustive but simply to present an overall view of the problem and to briefly mention some solutions. It should be easy to observe from the results disclosed in the different Tables (VI-XII) that the neutral heterosubstituted methyl-metal derivatives ( $XCH_2M$ ) are all presently known (with the probable exception of  $X:F$ , or  $R_2Bi$  in Eq. 125). The latest ones being described by Kauffmann<sup>274</sup> in November 1978. If one alkyl group is attached to the carbanionic center, the number of case described is clearly lowered and only very few  $\alpha$ -heterosubstituted carbanions bearing two alkyl groups (with the exception of the cyclopropyl case) can be found in the literature.

## IIA ADDITION REACTIONS

### IIA1 Addition of organometallics to heterosubstituted ethylenes (Eq. 124a, Table VIa)

This reaction mainly performed with alkyllithiums in ether is described in the cases of vinyl silanes,<sup>14\*, 15\*, 46, 340, 341</sup> vinyl phosphine,<sup>207</sup> vinyl sulfide,<sup>222, 223</sup> vinyl arsine<sup>231</sup> and vinyl selenide<sup>136, 231, 233</sup> and vinyl germane<sup>487</sup> (Table VIa).

Table VIa.



			solvent	°C	Time (hr)	Yield (%)	REF.
a	BuLi	$CH_2 = CH-Si(C_6H_5)_3$	ether	—	1.25	77	46, 340
b	$(CH_3)_2CHMgCl$	$CH_2 = CH-Si(CH_3)_2OC_2H_5$	ether	36	16	98	341
c	BuLi	$CH_2 = CH-P(C_6H_5)_2$	ether	-10	6	58	207
d	BuLi	$CH_2 = CH-SC_6H_5$	ether	0	4	56	222, 223
e	BuLi	$CH_2 = CH-As(C_6H_5)_2$	THF	20	0,5	95	231
f	BuLi	$CH_2 = CH-SeC_6H_5$	ether	20	1	65-72	136, 231, 233
g	BuLi	$CH_2 = CH-halogen$				unknown	
h	$C_6H_5Li$	$CH_2 = CH-Ce(C_6H_5)_3$	ether	20	16	60	487

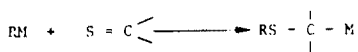
Concurrent reactions namely the metallation reaction leading to  $\alpha$  or  $\gamma$  metallo  $\alpha$ -heterosubstituted olefins or to the cleavage of the carbon-heteroatom bond is sometimes noticed. The first reaction usually occurs with derivatives in which the heteroatom belongs to the second row of the Periodic Table (i.e. in case of vinyl ethers,<sup>126-131</sup> It has also been observed in case of vinyl sulfides when a more polar solvent is used (i.e. sec BuLi in THF-HMPT, instead of ether)<sup>132</sup> or when an organopotassium derivative instead of lithium is used.<sup>129</sup> The cleavage of the carbon-heteroatom bond is usually observed in case of vinyl halides<sup>1\*, 33\*</sup> producing  $\alpha$ -metallo olefins and in the case of vinyl phenyl selenide and n-BuLi when THF is used<sup>136, 233</sup> instead of ether.

The addition reaction of organometallic thus suffers from the restrictions already presented. It is moreover exclusively described for heterosubstituted ethylenes and disallows the synthesis of  $\alpha$ -heterosubstituted organometallics in which the carbanionic center bears two hydrogens or two alkyl groups.

### IIA2 Addition of organometallics onto an heteroatom doubly linked to a carbon atom (Eq. 124b, Table VIb)

This reaction is at present exclusively restricted to thiones which add alkyllithiums and magnesium usually in THF<sup>342\*, 343</sup> producing even dialkylsubstituted organometallics. Unfortunately these derivatives (which could be radicals)<sup>344</sup> have not yet been used as synthetic intermediates.

Table VI.B.

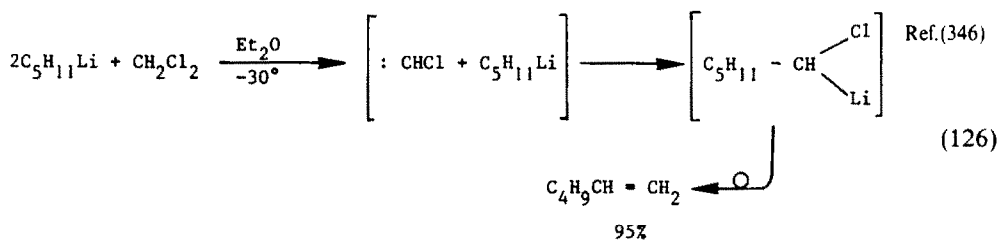


	conditions	°C	time (hr)	Yield(%)	REF.
$C_2H_5MgBr + S = C \begin{array}{l} \diagup \text{CH}_3 \\ \diagdown \text{C}_4H_9 \end{array}$	ether	20	3	2	343
	THF	20	3	90	343
$C_2H_5MgBr + S = C \begin{array}{l} \diagup \text{iC}_3H_7 \\ \diagdown \text{iC}_3H_7 \end{array}$	ether	20	3	2	343
	THF	20	3	83	343

\*Some of these compounds may not be carbanions but radicals

### IIA3 Addition of organometallics to carbenes (Eq. 124c)

This reaction seems to be unknown<sup>345</sup> § although  $\alpha$ -chlorohexyllithium has been postulated<sup>346</sup> as an intermediate in the formation of 1-hexene from dichloromethane and n-pentyllithium (Eq. 126).



### IIB EXCHANGE REACTIONS

They include very different reactions such as hydrogen-metal exchange, metal-metal exchange, metalloide-metal exchange and halogen-metal exchange.

#### IIB1 Hydrogen-metal exchange—metallation reaction (Eq. 125a, Table VII)

It is the most documented method for  $\alpha$ -heterosubstituted carbanions synthesis. It profits by the wide availability of the starting materials, the possibility of enhancing the acidity of " $\alpha$  hydrogen" either by changing the other groups directly attached to the heteroatom (except in case of halides) (Chapter IA2c) or by allowing the heteroatom to bear a partial or a full positive charge (Chapter IA2c). It also profits from the availability of several basic systems (base modulated by the solvent and additives).

(a) *The basic systems.* We have already discussed in Chapter IA4a the problems related to the base itself and in Chapter IA5 the role of the solvent especially for metallation purposes. However, we have listed below some basic systems: ||

*Carbanionic bases.* t-BuLi-HMPT; t-BuLi-TMEDA-pentane; BuLi-HMPT; t-BuOK-BuLi-hexane; BuLi-TMEDA-pentane; BuLi-DABCO-THF; Me<sub>3</sub>SiCH<sub>2</sub>K-THF.

*Non-carbanionic bases.* N-lithiotetramethyl-piperidine (LiTMP) THF-HMPT, lithium diisopropylamide (LDA)-HMPT; LDA-t-BuOK-THF; LiTMP-THF; LDA-THF; lithium, sodium, potassium salts of hexamethyl disilazane; KH-THF; NaH-THF; KNH<sub>2</sub>; NaNH<sub>2</sub>; LiNH<sub>2</sub>.

In several instances, alkylolithiums which are the strongest base known act as nucleophiles and react on the heteroatom itself (Chapter I, A4 and A5 and Chapter II, B2, B3 and B4) or on the other groups directly attached to the heteroatom (below and Chapter IA4) especially when a carbonyl group is directly attached to the heteroatom. Addition of HMPT (Normant), †† DABCO

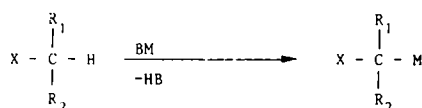
§ However the reverse process has been in several instances noticed<sup>33\*, 34\*, 81\*, 82\*, 83\*, 87, 186, 250, 281b, 467</sup>; see Chapter IA6).

¶ We will not discuss the case of metal-metal exchange such as alkali-alkali metal exchange, Li-Cu, Li-Hg exchange.

|| The basic systems are listed tentatively by decreasing order of basicity. However, this classification is subjected to caution.

†† Introduced in this field by

Table VII.

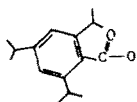


\* *r*, *A*, *B* refer respectively to hydrolisis alkylation and reaction with carbonyl compounds

	X	R <sub>1</sub>	R <sub>2</sub>	CONDITIONS	T°C	TIME (hour)	METAL	H <sup>+</sup> Yield %	A <sup>+</sup> Yield %	B <sup>+</sup> Yield %	ref.
a		H	H	tBuLi/pentane	+20°	256	Li	7,2	—	—	206
b		H	H	Sec BuLi/THF TMEDA	-78°	-0.1	Li	82	77	75	347
c		H	CH <sub>3</sub>	Sec BuLi/THF TMEDA	-45°	—	Li	—	—	55	347
d		H	H	Sec BuLi/THF TMEDA	0°	1.5	Li	—	87	63	348
e		H	H	Sec BuLi/THF HMPT	-100°	0.33	Li	80	59	68	349
f		H	H	Sec BuLi/THF TMEDA	-78°	0.5	Li	—	82	63	350
g	ON-N-CH <sub>3</sub>	H	H	LDA/THF	-78°	0.16	Li	—	95	85	298, 351
h	ON-NC <sub>2</sub> H <sub>5</sub>	H	H	LDA/THF	-80	0.16	Li	—	—	76	351, 352
i	ON-N-iC <sub>3</sub> H <sub>7</sub>	H	H	LDA/THF	-80	0.16	Li	—	97	85	351, 352
j	ON-N-tC <sub>4</sub> H <sub>5</sub>	H	H	LDA/THF	-80	0.16	Li	—	95	95	351, 352
k	ON-N-	H	H	LDA/THF	-80	0.16	Li	—	—	93	351
l	ON-N-	H	H	LDA/THF	-80	0.16	Li	—	58	60	351, 352
m	ON-N-C <sub>6</sub> H <sub>13</sub>	H	C <sub>5</sub> H <sub>11</sub>	LDA/THF	-80	0.16	Li	—	95	—	352, 353
n	ON-N-iC <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	CH <sub>3</sub>	LDA/THF	-80	0.16	Li	—	—	40	352
o				LDA/THF	-78	0.16	Li	—	—	65	353
p				LDA/THF	-78	0.16	Li	—	52	85	353, 354
q				LDA/THF/ether	-95; -78	1; 5	Li	—	85	—	354
r	C≡N-	H	H	BuLi/THF	-70	0.25	Li	—	—	80	355, 356
s	C≡N-	H	CH <sub>3</sub>	LTMP/THF	-70	0.5	Li	—	—	40	356
t	C≡N-	H	C <sub>2</sub> H <sub>5</sub>	BuLi/THF	-70	—	Li	—	—	10	355
u	C≡N-	CH <sub>3</sub>	CH <sub>3</sub>	LTMP/THF	-70	0.5	Li	—	—	5	356

X	R <sub>1</sub>	R <sub>2</sub>	CONDITIONS	T°C	TIME (hour)	METAL	H <sup>+</sup> Yield %	A <sup>+</sup> Yield %	B <sup>+</sup>	réf.
v C ≡ N-	CH <sub>2</sub> —CH <sub>2</sub>		BuLi/THF	-70	0.25	Li	65	75	356	
w C ≡ N-	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C	CH <sub>2</sub>	LDA/THF	-72	0.5	Li	70	96	—	277
x C ≡ N-	"		tBuONa/THF	-72	0.5	Na	78	—	—	277
y C ≡ N-	"		tBuOK/THF	-72	0.5	K	90	—	—	277
z C <sub>6</sub> H <sub>5</sub> CH = N	H	C <sub>6</sub> H <sub>5</sub>	LDA/THF-ether	-60	—	Li	—	—	86	357, 358*
aa (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C=N	H	H	LDA/THF-ether	-60	—	Li	75	64	52	357, 358*
ab (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C=N	H	H	Et <sub>2</sub> NLi/HMPT-C <sub>6</sub> H <sub>6</sub>	-70	1.5	Li	—	81	—	359
ac (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> C=N	H	H	BuLi/THF	-78	0.33	Li	—	88	85	359
ad C <sub>8</sub> H <sub>17</sub> N = N	H	H	LiN(Si(CH <sub>3</sub> ) <sub>3</sub> ) <sub>2</sub> /THF	0	0.8	Li	60	—	—	360
ae NO <sub>2</sub>	H	H	KF/iC <sub>3</sub> H <sub>7</sub> OH	+23	6	K	—	—	90	361
af NO <sub>2</sub>	H	C <sub>3</sub> H <sub>7</sub>	HN(iC <sub>3</sub> H <sub>7</sub> ) <sub>2</sub> /CHCl <sub>3</sub>	+60	—	Ni	—	—	90	139b
ag NO <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	HN(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> /CH <sub>3</sub> OH	+30	—	Ni	—	—	77	362
ah NO <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	LiOC <sub>2</sub> H <sub>5</sub> /C <sub>2</sub> H <sub>5</sub> OH	+20	—	Li	95	95	—	363, 364*
ai <sup>+</sup> NO <sub>2</sub>	H	H	2eq BuLi/THF-HMPT	-90	—	Li	—	—	65	365
aj <sup>+</sup> NO <sub>2</sub>	H	iC <sub>3</sub> H <sub>7</sub>	2eq BuLi/THF-HMPT	-90	—	Li	—	—	75	365

(B)



a	H	H	SecBuLi/THF-TMEDA	-95	2	Li	65	84	69	366
b	H	CH <sub>3</sub>	SecBuLi/THF-TMEDA	-75	2	Li	48	—	—	366

+ refers to dimetallated species


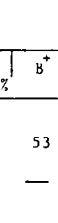
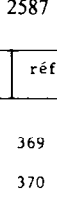
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
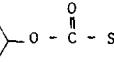
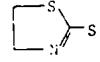
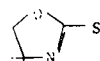
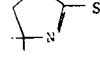
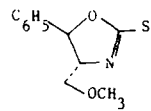
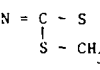




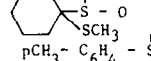
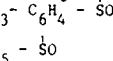




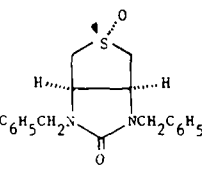
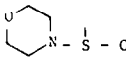









a (CH <sub>3</sub> ) <sub>3</sub> Si	H	li	BuLi/ether	+20	72	Li	—	00	—	275
b (CH <sub>3</sub> ) <sub>3</sub> Si	H	li	BuLi/TMEDA-pentane	+20	72	Li	—	36	—	275, 367
c (CH <sub>3</sub> ) <sub>3</sub> Si	H	H	tBuLi/TMEDA-pentane	+25	96	Li	—	40	—	276a, 367
d (CH <sub>3</sub> ) <sub>2</sub> SiC <sub>4</sub> H <sub>9</sub>	H	H	BuLi/TMEDA	+20	96	Li	—	46	—	275, 367
e (CH <sub>3</sub> ) <sub>2</sub> SiCl	H	H	tBuLi/THF	-78	2	Li	—	33	—	276a, 367
f (CH <sub>3</sub> ) <sub>2</sub> SiCl	H	H	tBuLi/TMEDA-pentane	+15+30	0.03	Li	—	20	—	276a, 367
g (CH <sub>3</sub> ) <sub>2</sub> SiOC <sub>2</sub> H <sub>5</sub>	H	H	tBuLi/TMEDA-pentane	+25	48	Li	—	50	—	276a, 367
h (CH <sub>3</sub> ) <sub>2</sub> -SiOSi(CH <sub>3</sub> ) <sub>3</sub>	H	H	tBuLi/pentane	—	96	Li	—	85	—	276b
i (CH <sub>3</sub> ) <sub>2</sub> SiOSi(CH <sub>3</sub> ) <sub>3</sub>	H	H	tBuLi/TMEDA	+25	264	Li	—	30	—	276a
j (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> Si	H	H	BuLi/TMEDA	+20	72	—	—	00	—	368

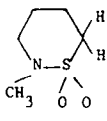
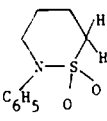
(D)

a (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> P	H	H	BuLi/pentane	+20	48	Li	0	—	—	206
b "	H	H	BuLi/ether	+20	48	Li	20	—	—	206
c "	H	H	BuLi/THF-TMEDA	+20	1	Li	84	—	—	187
d "	H	H	tBuLi/pentane	+20	312	Li	36	—	—	206
e (C <sub>6</sub> H <sub>5</sub> )P-CH <sub>3</sub>	H	H	tBuLi/pentane	+20	120	Li	54	—	—	187
f	H	H	BuLi/THF-TMEDA	+20	1	Li	65	—	—	187
g	H	H	BuLi/THF-TMEDA	+20	4.5	Li	75	—	—	187
h (C <sub>6</sub> H <sub>13</sub> ) <sub>2</sub> P	H	H	tBuLi/pentane	+20	72	Li	46	—	—	206
i (C <sub>6</sub> H <sub>13</sub> )PCH <sub>3</sub>	H	H	BuLi/THF-TMEDA	+20	6	Li	63	—	—	187
j "	H	H	BuLi/THF-TMEDA	+20	41	Li	87	—	—	187



X	R <sub>1</sub>	R <sub>2</sub>	CONDITIONS	T°C	TIME (hour)	METAL	H <sup>+</sup>	A <sup>+</sup> Yield %	B <sup>+</sup>	réf.
k (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> P-C <sub>3</sub> H <sub>7</sub>	H	H	tBuLi/pentane	+20	93	Li	—	—	53	369
l (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> P	H	H	BuLi/THF-TMEDA CuCl	+20	—	Cu	—	40	—	370
m 	H	H	BuLi/Hexane-ether	$\Delta$	4	Li	—	—	64	371
n "	H	H	NaNH <sub>2</sub> /Benzene	+80	4	Na	—	—	96	372
o "	H	H	1)BuLi/THF 2)CuCl	-60 $\rightarrow$ 0°	—	Cu	—	75	—	370
p "	H	CH <sub>3</sub>	NaNH <sub>2</sub> /Benzene	+80	4	Na	—	—	51	372
q "	H	C <sub>2</sub> H <sub>5</sub>	BuLi/THF-TMEDA	-78	0.2	Li	—	62	—	143
r "	H	C <sub>3</sub> H <sub>7</sub>	1)BuLi/THF 2)CuCl	-60 $\rightarrow$ 0°	—	Cu	—	68	—	370
s "	H	iC <sub>4</sub> H <sub>9</sub>	BuLi/THF-TMEDA	-78	0.2	Li	—	78	—	143
-----										
t (CH <sub>3</sub> O) <sub>2</sub> P-O	H	H	BuLi/THF	-78	0.08	Li	—	—	high	45
u (CH <sub>3</sub> O)P-O	H	H	1)BuLi/THF 2)CuI	1)-70 2)-35	—	Cu	—	80	—	374,375
v (CH <sub>3</sub> O)P-O	H	CH <sub>3</sub>	BuLi/THF	-78	0.08	Li	—	—	high	45
w (C <sub>2</sub> H <sub>5</sub> O)P-O	H	H	1)BuLi/THF 2)CuI	1)-70 2)-35	—	Cu	—	100	—	374
x (C <sub>2</sub> H <sub>5</sub> O)P-O	H	CH <sub>3</sub>	1)BuLi/THF 2)CuI	1)-70 2)-35	1	Cu	—	87	—	375
y (C <sub>2</sub> H <sub>5</sub> O)P-O	H	CH <sub>2</sub> CH=CH <sub>2</sub>	1)BuLi/THF 2)CuI	1)-70 2)-35	1	Cu	—	75	—	375
z (CH <sub>3</sub> O) <sub>2</sub> P-S	H	H	BuLi/THF	-78	0.08	Li	—	—	81	45
aa (CH <sub>3</sub> O) <sub>2</sub> P-S	H	CH <sub>3</sub>	BuLi/THF	-78	0.33	Li	—	—	93	45
ab (CH <sub>3</sub> O) <sub>2</sub> P-S	H	C <sub>3</sub> H <sub>7</sub>	BuLi/THF	-78	0.5	Li	—	—	88	45
ac (CH <sub>3</sub> O) <sub>2</sub> P-S	CH <sub>3</sub>	CH <sub>3</sub>	BuLi/THF	-50	1.5	Li	—	—	80	45
ad [(CH <sub>3</sub> ) <sub>2</sub> N] <sub>2</sub> P-O	H	H	BuLi/THF	-78	0.25	Li	—	—	98	44,376*, 373
ae [(CH <sub>3</sub> ) <sub>2</sub> N] <sub>2</sub> P-O	H	H	LiNMe <sub>2</sub> /HMPA	-70	—	Li	—	—	96	377
af "	H	CH <sub>3</sub>	BuLi/THF	-50	2	Li	—	—	98	44,376*, 373
ag "	H	C <sub>7</sub> H <sub>15</sub>	BuLi/THF	-70	4	Li	—	—	97	373,376*
ah "	CH <sub>3</sub>	CH <sub>3</sub>	BuLi/THF	-40	5	Li	—	—	94	373,376*
-----										
<b>(E)</b>										
a CH <sub>3</sub> S	H	H	BuLi/Hexane-TMEDA	+20	4	Li	—	59	84	218,381
b C <sub>6</sub> H <sub>5</sub> S	H	H	BuLi/ether	+36	15	Li	—	—	43	378,379
c C <sub>6</sub> H <sub>5</sub> S	H	H	BuLi/THF-DABCO	0	0.8	Li	97	—	93	208,380
d C <sub>6</sub> H <sub>5</sub> S	H	H	C <sub>6</sub> H <sub>5</sub> Li/THF	+25	15	Li	—	—	90	208
e C <sub>6</sub> H <sub>5</sub> S	H	H	tBuLi/THF-HMPT	-78	3	Li	100	—	—	209
f C <sub>6</sub> H <sub>5</sub> S	H	H	1)C <sub>6</sub> H <sub>5</sub> Li/THF 2)CuI	-50	1	Cu	—	58	—	250
g CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> S	H	H	BuLi/ether	—	—	Li	—	67	—	378
h C <sub>6</sub> H <sub>5</sub> S	H	CH(CH <sub>3</sub> ) <sub>2</sub>	tBuLi/THF-HMPT	-78	3	Li	100	79	92	209
i C <sub>6</sub> H <sub>5</sub> S	H	(CH <sub>2</sub> ) <sub>2</sub> Cl	KNH <sub>2</sub> /NH <sub>3</sub> -ether	-20	3	K	—	74	—	382
j C <sub>6</sub> H <sub>5</sub> S	-CH <sub>2</sub> -	-CH <sub>2</sub> -	BuLi/THF	0	2	Li	—	—	92	302,383
k 	H	H	BuLi/THF	-78	—	Li	87	86	80	347
	H	CH <sub>3</sub>	Sec BuLi/THF-TMEDA	-95	—	Li	—	—	89	347b
l 	H	CH <sub>3</sub>	Sec BuLi/TMEDA	-95	—	Li	—	—	86	347


X	R <sub>1</sub>	R <sub>2</sub>	CONDITIONS	T°C	TIME (hour)	METAL	H <sup>+</sup>	A <sup>+</sup> Yield %	B <sup>+</sup>	réf.
m 	H	H	LDA/THF	-78	0.5	Li	—	—	77	80,384
n 	H	H	LDA/THF	-78	1	Li	—	—	71	80,384
o 	H	H	BuLi/THF	-20	0.5	Li	—	70	73	80,171
p 	H	H	BuLi/THF	-78	2	Li	—	93	78	79,387,3
q 	H	CH <sub>3</sub>	BuLi/THF	-78	2	Li	—	—	0	79,388 <sup>M</sup>
r 	H	H	LDA/THF	-78	2	Li	—	81	70	79,387,3
s 	H	H	LDA/THF	-70	—	Li	—	75	80	263
t 	H	H	tBuOK/DMSO	+70	1	K	—	—	72	389,390
u 	H	H	NaH/DMSO	+70	0.8	Na	—	98	86	62
v 	H	H	NaNH <sub>2</sub> /DMSO	+70	0.8	Na	—	98	100	62
w 	H	H	CH <sub>3</sub> Li/THF	-60	—	Li	—	—	98	53
x 	H	H	LiNEt <sub>2</sub> /THF	-15	0.3	Li	—	—	96	393
y 	H	H	LiNEt <sub>2</sub> /THF	-10	—	Li	—	—	84	394,395
z 	H	CH <sub>3</sub>	CH <sub>3</sub> Li/THF	-60	—	Li	—	—	81	396
aa 	H	CH <sub>3</sub>	CH <sub>3</sub> Li/THF	-60	—	Li	—	—	98	53,396
ab 	H	C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub> Li/THF	-60	—	Li	—	—	96	53
ac 	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub> Li/THF	-60	—	Li	—	—	97	53
ad 	H	H	BuLi/THF	-78	—	—	—	30	—	270
ae 	H	H	tBuLi/THF	-70	rapid	Li	—	—	50	397
af 	H	H	BuLi/THF	-90	—	Li	—	—	50	56
ag 	H	H	2eq BuLi/THF	-78	0.3	Li	—	—	97	397
ah 	H	H	2eq BuLi/THF	-78	0.3	Li	—	—	100	56,397
ai 	H	CH <sub>3</sub>	2eq BuLi/THF	-40	0.2	Li	—	—	55	56,397
aj 	H	H	NaCH <sub>2</sub> -S <sup>O</sup> -CH <sub>3</sub> /DMSO	+20	1	Na	—	—	56	398
ak 	H	H	NaCH <sub>2</sub> SCH <sub>3</sub> /DMSO	+20	1	Na	—	—	65	398
al 	H	CH <sub>3</sub>	NaCH <sub>2</sub> SCH <sub>3</sub> /DMSO	+20	1	Na	—	—	65	398
am 	H	H	tBuLi/THF	-78	1	Li	—	unstable	—	56,397
an 	H	H	C <sub>2</sub> H <sub>5</sub> MgBr/benzene-ether	-78,+20	0.05	MgBr	—	100	—	399

X	R <sub>1</sub>	R <sub>2</sub>	CONDITIONS	T°C	TIME (hour)	METAL	H <sup>+</sup>	A <sup>+</sup> Yield %	B <sup>+</sup>	ref.
ap C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	H	H	NaOH 50% TEBA/CH <sub>2</sub> Cl <sub>2</sub>	+25	0.3	N=	—	—	86	400
aq C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	H	H	1) BuLi/THF 2) Cu <sub>2</sub> Cl <sub>2</sub>	0, -30		Cu	—	65	—	370
ar C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	H	(CH <sub>2</sub> ) <sub>9</sub> .COOH	1) 2 BuLi/THF	-20	0.2	Li	—	70	—	173
as C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	BuLi/THF	-78, +20	0.5	Li	—	94	—	401
at C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	H	C <sub>6</sub> H <sub>13</sub>	BuLi/THF	-78, 0	2	Li	—	87	—	173
au C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	RLi/THF-hexane	-70	—	Li	—	—	52	55
av C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	Mg/ether-benzene	-70	—	Mg	—	—	52	55
aw C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	CH <sub>3</sub>	(CH <sub>2</sub> )CH(OCH <sub>3</sub> ) <sub>2</sub>	BuLi/THF	-75	—	Li	—	87	—	402
ax C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	BuLi/THF	-78, 0	2	Li	—	78	—	173
ay C <sub>6</sub> H <sub>5</sub> -S(=O)-NCH <sub>3</sub>	H	H	BuLi/THF	0, 20	2	Li	—	—	90	404
az "	H	CH <sub>3</sub>	BuLi/THF	0, 20	2	Li	—	—	75	404
ba "	H	iC <sub>3</sub> H <sub>7</sub>	BuLi/THF	0, 20	2	Li	—	—	78	404
bb CH <sub>3</sub> -S(=O)-NTos	H	H	BuLi/DMSO	+20	—	Li	—	—	67	325
bc "	H	H	NaH/DMSO	+20	2-4	Na	—	—	84	325
bd C <sub>2</sub> H <sub>5</sub> -S(=O)-NTos	H	CH <sub>3</sub>	NaH/DMSO	+20	2-4	Na	—	—	62	325
be (CH <sub>3</sub> ) <sub>2</sub> CH-S(=O)-NTos	CH <sub>3</sub>	CH <sub>3</sub>	NaH/DMSO	+20	2-4	Na	—	—	63	325
bf										
bg C <sub>6</sub> H <sub>5</sub> -S(=O)-NTos	H	H	BuLi/THF	-78, +20	—	Li	—	—	86	325
bh	H	H	BuLi/DMSO	+20	—	Li	—	—	66	325
bi	H	H	NaH/DMSO	+20	2-4	Li	—	—	86	325
bj		CH <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub> -CH <sub>2</sub>	NaH/DMSO	+20	2-4	Na	—	—	39	325
bi		CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> -CH <sub>2</sub>	NaH/DMSO	+20	20	Na	—	—	34	325
bk C <sub>6</sub> H <sub>5</sub> -S(=O)-NTos	H	H	BuLi/THF	+20	2.4	Li	—	—	75	325
bl C <sub>6</sub> H <sub>5</sub> -S(=O)-NTos	H	H	NaH/DMSO	-70	0.4	Na	—	—	40	325
bm CH <sub>3</sub> O-SO <sub>2</sub> -	H	H	BuLi/THF	-78	—	Li	—	—	91	56, 397
bn (CH <sub>3</sub> ) <sub>2</sub> NSO <sub>2</sub>	H	H	2 eq. BuLi/THF	+20	1	Li	—	—	50	405
bo 			BuLi/THF-hexane	25	0.16	Li	—	65	91	406
bp 			BuLi/THF-hexane	25	0.16	Li	—	70	86	406

F

a (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> As-O	H	H	LDA/THF	-40	0.5	Li	—	72	82	407
b "	H	C <sub>2</sub> H <sub>5</sub>	LDA/THF	—	—	Li	—	72	—	408
c "	H	C <sub>4</sub> H <sub>9</sub>	LDA/THF	—	—	Li	—	51	93	408

G

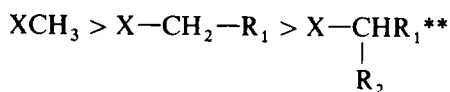
a C <sub>6</sub> H <sub>5</sub> Se	H	H	BuLi-TMEDA/THF	0	—	Li	—	—	38	186b
b C <sub>6</sub> H <sub>5</sub> SeO	H	H	LDA/THF or ether	-78	—	Li	—	75	—	57, 409
c C <sub>6</sub> H <sub>5</sub> SeO	H	(CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	LDA/THF or ether	-78	0.3	Li	—	64	81	57, 409
d C <sub>6</sub> H <sub>5</sub> SeO	H		LDA/THF or ether	-78	—	Li	—	—	50	409
e C <sub>6</sub> H <sub>5</sub> SeO	CH <sub>3</sub>	CH <sub>3</sub>	LDA/THF or ether	-78	—	Li	—	—	81	57, 409

X	R <sub>1</sub>	R <sub>2</sub>	CONDITIONS	T°C	TIME (hour)	METAL	H <sup>+</sup>	A <sup>+</sup> Yield %	B <sup>+</sup>	réf.
<b>(H)</b>										
a	(CH <sub>3</sub> ) <sub>3</sub> N <sup>+</sup> -	H	H	C <sub>6</sub> H <sub>5</sub> Li/ether	—	—	Li	—	—	15 417
b	(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> N <sup>+</sup> -C≡N <sup>-</sup>	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> Li/THF	0	0.1	Li	59	—	— 418
c	(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> N <sup>+</sup> -C≡N <sup>-</sup>	C <sub>5</sub> H <sub>11</sub>	C <sub>5</sub> H <sub>11</sub>	C <sub>6</sub> H <sub>5</sub> Li/THF	0	0.1	Li	78	—	— 418
<b>(I)</b>										
a	(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> S <sup>+</sup>	H	H	BuLi/ether	+20	—	Li	—	—	96 410
b	"	H	H	Na <sup>(*)</sup> (-) CH <sub>2</sub> -S <sup>O</sup> -CH <sub>3</sub> /DMSO	+20	0.166	Na	—	—	86 271
c	"	H	H	NaOH 5N/benzene	+40	24	Na	—	—	99 411
d	"	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> Li/ether	+20	3	Li	—	—	58 413
e	"	H	CH <sub>3</sub>	Na <sup>(*)</sup> (-) CH <sub>2</sub> -S <sup>O</sup> /DMSO	+20	0.25	Na	—	—	97 271
f	"	H	CH <sub>3</sub>	NaOH 5N/benzene	+20	24	Na	—	—	46 411
g	"	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> Li/ether	—	—	Li	—	—	68 413
h	"	CH <sub>3</sub>	CH <sub>3</sub>	BuLi/THF	-78, -10 or +20	0.16, 1 0.5	Li	—	—	67 97,98
i	"	CH <sub>2</sub> — CH <sub>2</sub>	CH <sub>2</sub> — CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> Li/ether	—	—	Li	—	—	68 414
j	"	CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub>	CH <sub>2</sub> - CH <sub>2</sub> - CH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> Li/ether	(+20)	2	Li	—	—	57 415
k	"	CH <sub>3</sub>	CH - C <sub>6</sub> H <sub>13</sub> O-Li	BuLi/THF	-78, 0	—	Li	—	—	73 416
<b>(J)</b>										
a	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup> -	H	H	BuLi/THF	0, +25	0.2, 1	Li	—	—	77 62
				NaCH <sub>2</sub> -S <sup>O</sup> -CH <sub>3</sub> /DMSO	+5	0.05	Na	—	—	84 62
				tBuOK/DMSO	+25	1	K	—	—	82 63,415
				NaOH 50% H <sub>2</sub> O/CH <sub>2</sub> Cl <sub>2</sub> TBAI	+50	48	N <sup>+</sup>	—	—	90 66
b	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> S <sup>+</sup> -	H	CH <sub>3</sub>	BuLi/THF	-76	0.5	Li	—	—	50 420
				tBuLi/THF	-76	0.5	Li	—	—	74 420
				LDA/THF	-78	—	Li	—	—	71 420
c	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> S <sup>+</sup> -	CH <sub>3</sub>	CH <sub>3</sub>	LiCHCl <sub>2</sub> /DME	-70	1	Li	—	—	82 64,91
				tBuLi/THF	-78	—	Li	—	—	60 64,91
				tBuLi/THF	-50	1	Li	—	not given	91
d	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> S <sup>+</sup> -	CH <sub>2</sub> — CH <sub>2</sub>	CH <sub>2</sub> — CH <sub>2</sub>	KOH/DMSO	+25	18	K	—	—	92 423
				NaCH <sub>2</sub> -S <sup>O</sup> -CH <sub>3</sub> /DMSO-DME	-45	0.06	Na	—	—	90 421
e	CH <sub>3</sub> -S <sup>O</sup> -N(CH <sub>3</sub> ) <sub>2</sub>	H	H	NaH/DMSO	+25	—	Na	—	—	60 320b
f	C <sub>6</sub> H <sub>5</sub> -S <sup>O</sup> -N(CH <sub>3</sub> ) <sub>2</sub>	H	H	NaH/DMSO	+25	—	Na	—	—	84 320
g	pCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -S <sup>O</sup> -N(CH <sub>3</sub> ) <sub>2</sub>	H	H	NaH/DMF	0, +25	0.01, 0.5	Na	—	—	95 71
h	pCH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> -S <sup>O</sup> -N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>3</sub>	CH <sub>3</sub>	NaH/DMF	0, +25	0.01, 0.5	Na	—	—	85 71
i	C <sub>6</sub> H <sub>5</sub> -S <sup>O</sup> -N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> — CH <sub>2</sub>	CH <sub>2</sub> — CH <sub>2</sub>	NaH/DMSO	+25	20	Na	—	—	89 71
j	(CH <sub>3</sub> ) <sub>2</sub> S <sup>+</sup> -O	H	H	NaCH <sub>2</sub> -S <sup>O</sup> -CH <sub>3</sub> /DMSO	+50	1	Na	—	—	90 62
<b>(K)</b>										
a	(CH <sub>3</sub> ) <sub>2</sub> Se <sup>+</sup>	H	H	LiCH <sub>2</sub> Cl/DME	-78	—	Li	—	—	30 68
b	(CH <sub>3</sub> ) <sub>2</sub> Se <sup>+</sup>	H	H	tBuOK/DMSO	+20	2	K	—	—	90 68
c	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> Se <sup>+</sup>	H	H	tBuOK/DMSO	+20	2	K	—	—	90 68
d	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> Se <sup>+</sup>	H	CH <sub>3</sub>	tBuOK/DMSO	+20	2	K	—	—	69 68

(Corey),<sup>††</sup> TMEDA (Peterson)<sup>††</sup> in the medium increases the basic reactivity of the alkyllithiums at the expense of their nucleophilicity [cf for example: in the case of phosphines<sup>267</sup> (Eq. (130), entry b to a; d to c; g to f); and in the case of selenides (Eq. (136), entry i<sup>186</sup> to entry b<sup>229</sup> and c<sup>425</sup>]. Another solution to this problem is the use of N metallated bulky amides which are less basic than alkyl lithiums but are less prone to react as nucleophiles. Thus they have been widely used any time a nucleophilic reaction has to be avoided.

(b) *Examples of metallation reaction.* The success of the metallation reaction is of course, as already discussed, directly related to the choice of the right basic system, but above, depends on the structure of the starting material to be metallated. We have already discussed the role of the heteroatom and of the heteroatomic moiety for the stabilization of the carbanionic center (Chapter IA2). We will discuss the problem related to the metallation of the different derivatives according to the lines presented in Chapter IA2.

We must again tell that we will restrict ourselves to the cases of derivatives which bear two hydrogens or alkyl groups on the site to be metallated. They are generally the less stabilized ones and it can be observed from the results disclosed in Table VII that whatever is the heteroatomic moiety, the ease of metallation widely decreases in the following order:



( $\alpha$ ) *The neutral heteroatom is not attached to another group (halogens) or is directly attached to an alkyl or a phenyl group (Table VII).*

Only a few examples of this kind have been disclosed even when the site to be metallated bear two hydrogens: simple alkylhalides have not been metallated in  $\alpha$  position and methylamines are metallated in very low yield by the strongly basic t-butyllithium (Table VIIA, a)<sup>206</sup> or with n-butyllithium-TMEDA.<sup>275</sup>

Dialkylethers are metallated with alkyllithiums near 0°, <sup>273</sup> the reaction is slow with diethyl ether but much more rapid in case of THF (halftime: 0.3 hr with n-BuLi; 0.05 hr with t-BuLi.<sup>267</sup> Unfortunately, the resulting carbanions do not survive at this temperature and cannot be further used in synthesis. Methylphenyl ether is exclusively metallated on the benzene ring<sup>285</sup> and the anion does not isomerise to the phenoxy methylithium. Methylsilanes (Table VII, entry C),<sup>14\*,15\*</sup> methyl phosphines (Table VIID, a-e, Eq. 130) and methyl sulfides (Table VIIE, a-g) in which the heteroatom belongs to the third row in the periodic table and methyl phenyl selenide require at least n-BuLi-TMEDA or n-BuLi-DABCO for their successful metallation and methyltriphenyl arsine<sup>231</sup> is reluctant to metallation. Except the unprecedented case of triphenyl methylsilane, which is not metallated (Table VIIC, j)<sup>368</sup> under conditions which allow the metallation of tetramethylsilane,<sup>275,367</sup> the presence of a phenyl group directly attached to the heteroatom enhances the acidity of the starting derivative. However, in several instances metallation occurs on the phenyl group<sup>136, 208, 209, 267, 286</sup> or kinetically<sup>208, 286</sup> or thermodynamically.<sup>136, 209, 286</sup> Phenyl-(primary alkyl) sulfides which are quantitatively deprotonated<sup>209</sup> with t-butyllithium in THF-HMPT (Table VIIE, h) but not with n-BuLi-TMEDA or DABCO (cf with Table VII, entry E h to E a, E c) are the only  $\alpha$ -heterosubstituted carbanions<sup>††</sup> bearing an alkyl group on the carbanionic center prepared by metallation reaction. §§ There is no example of successful synthesis of any related dialkylsubstituted carbanion using similar reaction.

( $\beta$ ) *The heteroatom is attached to groups which stabilize the carbanion by charge-dipole interactions (Table VII).*

Ion-dipole interaction is one of the interesting ways to stabilize an  $\alpha$ -heterosubstituted carbanion. Much work was done in this field by P. Beak who recently reviewed<sup>10\*</sup> the subject.

Several successful metallations have been described when N, O and S atoms are directly attached to a CO group such as in N,N-dimethyl- and N,N-diethyl-amides (Table VIIA, b, c),<sup>347</sup> N,N-dimethyl thioamide (Table VIIA, f)<sup>350</sup> and N-methylsuccinimides (Table VIIAe),<sup>349</sup> in methyl and ethyl esters (Table VIIB, a, b),<sup>366</sup> methyl and ethyl thioesters (Table VIIE, k, l)<sup>347</sup> derived from aromatic

\*\* When R<sub>1</sub> and R<sub>2</sub> are part of a three membered cycle, the metallation is easier, sometimes easiest than if R<sub>1</sub> and R<sub>2</sub> are hydrogen. The corresponding carbanions are listed in Table VII but will not appear in the discussion.

†† Bearing a non-charged heteroatom on the other side to alkyl or phenyl groups.

§§ 1-(3-Chloro, propanyl) phenyl sulfide is cyclised with potassium amide in ammoniac ether.<sup>382</sup>

carboxylic acids; and finally in N-methylcarbamate (Table VIIA, d)<sup>348</sup> and methylthio carbonates (Table VIIE, m, n)<sup>80,384</sup>

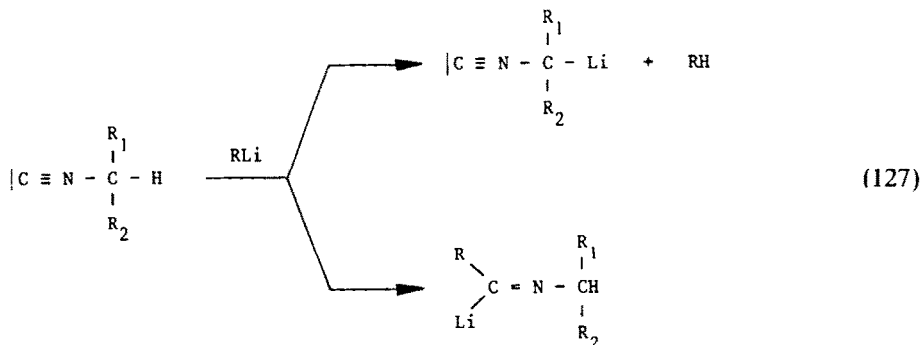
In all the cases, the CO group has to be well protected,<sup>¶¶</sup> by bulky groups, against the attack of the base acting as nucleophile or against the reaction of the carbanion itself once it is formed (which leads to dimeric products).

When the heteroatom is sulfur, similar acidification of the Me group (at the exclusion of the ethyl or higher homologs) has been achieved when it is attached to an oxazoline (Table VIIE p, q, r),<sup>79,387,388\*</sup> an iminothiocarbonate (Table IIE, s)<sup>263</sup> or a thiazoline (Table VIIE, o),<sup>80,385,386</sup>

Finally, N-nitrosamines introduced at a synthetic level by Seebach and Enders<sup>11\*</sup> and isocyanides developed by Scholkopf<sup>355</sup> and recently reviewed<sup>5\*,12\*</sup> are also useful starting material for  $\alpha$ -metallated nitrogen derivatives.

The nitrosamine route is by far the most powerful route to  $\alpha$  nitrogen substituted carbanions synthesis since the starting material is very easily prepared,<sup>11\*</sup> easily metallated (Table VIIA, g-q)<sup>11\*</sup> and rapidly transformed back to free amines.<sup>11\*</sup> Lithium diisopropylamide in THF is suitable for quantitative metallation of N-methyl (Table VIIA, g-k)<sup>11\*,351,352,354</sup> and N-alkyl or cyclic nitrosamines (Table VIIA, m, o-q)<sup>11\*,352-354</sup> but under the same condition N,N-diisopropyl N-nitrosamine is metallated in much lower yield (Table VIIA).<sup>11\*,352</sup> It has also been described<sup>11\*</sup> that  $\alpha$ -lithionitrosamides in THF decompose with a half life of 2 hr and that addition of four equivalents of HMPT increases their stability (half-life 4 hr).

N-methyl isocyanide is easily deprotonated by n-BuLi (Table VIIA, r)<sup>355,356</sup> whereas higher homologs are much less acidic and are metallated in low [N-n alkyl isocyanides 40%-10%] (Table VIIA, s, t)<sup>355,356</sup> or symbolic yield [(N-isopropyl isocyanide 5%)] (Table VIIA, u)<sup>356</sup>. The low yields observed in those cases are probably due to the competing addition of the alkyl lithiums generally required for metallation purposes (Eq. 127).



( $\gamma$ ) *Stabilization by delocalization of the negative charge* (Table VII).

This type of stabilization has been achieved in the case of nitrogen derivatives. Thus N-methyl imines derived from benzaldehyde (Table IIA, z)<sup>357,358\*</sup> or benzophenone (Table VIIA, aa, ab, ac)<sup>357,358\*,359</sup> are easily metallated by LDA in THF-ether, LDA in HMPT-benzene or by n-BuLi in THF; however, there is no mention of successful metallation of higher homologs.

( $\delta$ ) *Stabilization by a charged or partially charged heteroatom.*

Activation of an heteroatom, when possible by introduction of a partial or a full positive charge is one of the best way to acidify several derivatives bearing such heteroatom.

Thus whereas ethyl-arsines, -phosphines, -selenides and isopropyl analogues including isopropylsulfide are not metallated, even under drastic conditions (Chapter IIB1 (†)), the corresponding derivatives in which the heteroatom is oxidized are quite easily deprotonated. That is the case of phosphinioxides (Table VIID, m-s),<sup>9\*,16\*,17\*,45-375</sup> phosphonates (Table VIID, t-y),<sup>9\*,16\*,17\*,45-375</sup> phosphothiolates (Table IID, z-ac),<sup>45</sup> phosphonamides (Table VIID, ad-ah),<sup>44,373,376\*,377</sup> sulfoxides (Table VIIE, t-ad),<sup>53,62,270,389-391,393-396</sup> sulfinylamides (Table VIIE, ae-ai),<sup>56,397</sup> N-tosyl sulfinimides (Table VIIE, aj-al).<sup>398</sup>

Even higher acidification is observed in sulfones (Table VIIE, an-ax),<sup>26\*,27\*,55,173,370,399-402</sup> sulfoximines (Table VIIE, ay-bl),<sup>69\*,325,404</sup> sulfoxamides (Table VIIE, bn-bp)<sup>405,406</sup> and above all

<sup>¶¶</sup> This protection however has the great disadvantage to disallow the easy deprotection after further reactions of the carbanion with electrophiles. For one solution to this problem see Refs. 80, 348.

in nitroalkanes (Table VIIA, ae-aj).<sup>139, 361-363, 364\*, 365</sup> In the later case, successful dimetallation has been recently described (Table VIIA, ai-aj).<sup>365</sup>

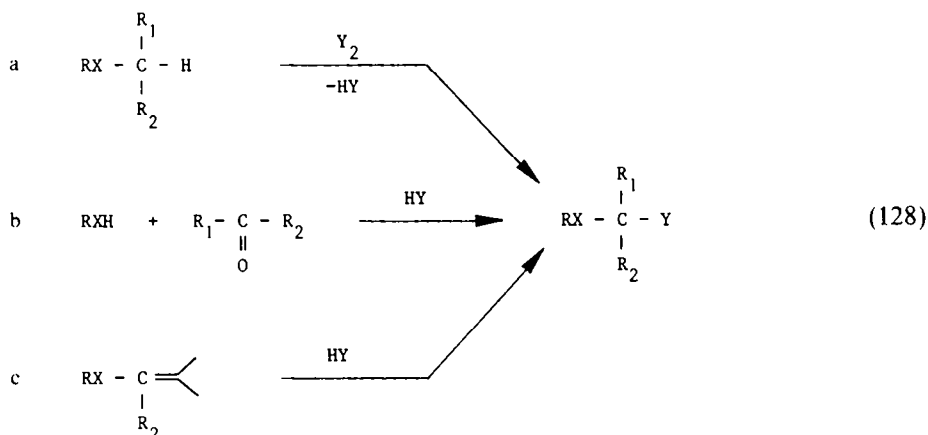
Finally, we must mention the ylide formation when ammoniums salts (Table VIIIH, a-c),<sup>9\*, 417, 418\*</sup> phosphonium salts (Table VII, a-h),<sup>9\*, 16\*, 22\*, 97, 98, 271, 410-416</sup> sulfonium salts (Table VIIIJ, a-d)<sup>9\*, 23\*, 28\*, 62-66, 91, 419-421, 423</sup> and dialkyl-amino sulfonium salts (Table VIIIJ, e-i),<sup>71, 320</sup> arsonium salts (Table VIIIJ),<sup>9\*</sup> selenonium salts (Table VIIK, a-d),<sup>68</sup> stibonium salts<sup>9\*</sup> are reacted with bases.

Several of these carbanions have been used as powerful building blocks for olefins and epoxides synthesis (with a new carbon-carbon bond formation) from carbonyl compounds.

### IIB2 Halogen-metal exchange (Eqn 125d Table VIII)

Halogen-metal exchange can be achieved by reaction of  $\alpha$ -heterosubstituted alkylhalides with the metal itself or with a suitable organometallic: generally an alkyllithium (butyl or t-butyllithium), or isopropyl magnesium halide.

The reaction is mainly restricted at present time by the unavailability of the starting material which can be prepared in some cases from the heterosubstituted alkanes and halogenes or N halogenosuccinimides (Eq. 128a); from carbonyl compounds (Eq. 128b), or by addition of hydrogen halides to  $\alpha$ -heterosubstituted olefins (Eq. 128c).



(a) The reaction of  $\alpha$ -heterosubstituted alkylhalides with the metal itself (Table VIIIa) is not the usual route for  $\alpha$ -heterosubstituted carbanions synthesis because, in many cases, the temperature required for the exchange reaction is too high to permit the conservation of the carbanion. One solution to this problem is the *in situ* synthesis of the organometallic in the presence of the electrophile which is related to this Barbier reaction (Table VIIIa, b, c, d, j).

Otherwise the reactions are heterogenous, require special sized particules containing traces of doping agent (Na, K) and their reproductibility is sometimes low.

Chloromethyl methylether is easily transformed to the corresponding organometallic when reacted with magnesium<sup>428, 429</sup> or lithium in methyllal (Table VIIIa, a, b) but not in THF<sup>426-429</sup> whereas the closely related chloromethylbenzylether reacts<sup>432</sup> with magnesium in THF (Table VIIIa, e).

The reaction of Zn-Cu couple with diiodomethane is one of the most famous representative example of this reaction allowing the synthesis of the carbanionic species<sup>434</sup> (Table VIIIa, f) acting as nucleophile or precursor of the corresponding carbene useful in cyclopropanation of olefins (Simons-Smith reaction).<sup>434</sup>

(b) Halogen-metal exchange using an organometallic as the metal source (eqn 125d, Table VIIIb). This reaction is a well known and a widely used one in the case of alkyl halides.<sup>1\*</sup>  $\alpha$ -Metallation reaction (leading to a carbene),  $\beta$ -elimination reaction (leading to an olefin) and substitution reactions are the competitive reactions. Another problem may arise from further alkylation of the just formed  $\alpha$ -heterosubstituted carbanion with the exchanged alkylhalide (see Chapter I A4, Eq. 85, 86<sup>2, 39</sup>). The halogen metal exchange in  $\alpha$ -heterosubstituted halides occurring at lower temperature than the others, lowering of the temperature usually favors the desired reaction.

The reaction can be reversible and is shifted toward the formation of the  $\alpha$ -heterosubstituted carbanion if the later precipitates out of the solution or when it is the best stabilized carbanion present.<sup>1\*</sup>

The synthesis of a specific  $\alpha$ -heterosubstituted organometallic usually occurs with  $\alpha$ -heterosubstituted bromides or iodides and rarely with chloride and fluorides (Table VIII B, cf a-c and e-f).<sup>368,74,219</sup> Alkylolithiums in ethers (better in THF) are the classical reagents but isopropyl magnesium halides have also been used (Table VIII B). Tertiary butyllithium (2 eq.) should have the advantage over the others alkylolithiums to destroy the exchanged alkylhalides displacing the equilibrium in the desired direction and preventing further substitution reaction to occur.<sup>239</sup>

Table VIII A.

$$\text{X} - \underset{\text{R}_2}{\overset{\text{R}_1}{\text{C}}} - \text{hal} + \text{M} \longrightarrow \text{X} - \underset{\text{R}_2}{\overset{\text{R}_1}{\text{C}}} - \text{M} + \text{MCl}$$

			temp.	time	yield(%)	REF.
				(hr)		
a	CH <sub>3</sub> OCH <sub>2</sub> Cl <sup>+</sup>	Li, (CH <sub>3</sub> O) <sub>2</sub> CH <sub>2</sub>	-30		80	426, 427
b	CH <sub>3</sub> OCH <sub>2</sub> Cl <sup>+</sup>	Mg, (CH <sub>3</sub> O) <sub>2</sub> CH <sub>2</sub>	0	3	51	428, 429
c	C <sub>2</sub> H <sub>5</sub> O-CH <sub>2</sub> Cl <sup>++</sup>	Mg/HgCl <sub>2</sub> , THF	0	3	90	430
d	C <sub>2</sub> H <sub>5</sub> O- $\underset{\text{CH}_3}{\text{CHCl}}$ <sup>++</sup>	Mg/HgCl <sub>2</sub> , THF	0	3	60	431
e	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> O-CH <sub>2</sub> Cl	Mg, THF	—	—	80	432
f	ICH <sub>2</sub> I	Zn/Cu, THF	40	3	94	433-435
g	(CH <sub>3</sub> ) <sub>3</sub> SiCH <sub>2</sub> Cl	Mg, ether	0	3	88	436
h	(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> SiCH <sub>2</sub> Br	Li, ether	36	20	17	368
i	CH <sub>3</sub> SCH <sub>2</sub> Cl	Mg, THF	36	—	33	437
j	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> S-CH <sub>2</sub> Cl	Mg, THF	—	—	50	432

+ using THF instead of methyllal leads to disappointing results

++ prepared in situ in presence of a carbonyl compound.

Several mechanisms have been proposed for halogen metal exchange reaction which include the variation on a four center transition state,<sup>1\*</sup> the intermediacy formation of a ate complex<sup>235a</sup> or an heterolytic substitution reaction.<sup>1\*,235b</sup> Several representative examples of such reaction are listed in Table VIII B. Particularly spectacular is the selective cleavage of the C-halogen bond in bromomethylgermane (Table VIII B, i),<sup>368</sup> iodomethylstannane (Table VIII B, m),<sup>440</sup> iodomethylplumbane (Table VIII B, n)<sup>274</sup> and bromoalkylselenides (Table VIII B, j-1)<sup>439</sup> in which both the C-halogen and the C-Ge, C-Sn, C-Pb or C-Se bonds cleavage are expected to occur (Chapter IIB34).

These results could be explained not only by the relative ease of the C-halogen compared to the C-heteroatom bond cleavage but also by the relative stabilization of the two possible carbanions resulting from each expected cleavage.

The C-Br bond cleavage (n-BuLi in THF) was successfully used for diversely substituted  $\alpha$ -phenylselenoalkyllithiums synthesis (even dialkyl substituted ones).<sup>439</sup> Both the closely related  $\alpha$ -methylselenoalkylbromides and  $\alpha$ -phenylselenoalkylchlorides do not behave similarly.<sup>232, 439</sup> In the later case, some C-Se bond cleavage is observed.<sup>439</sup>

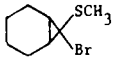

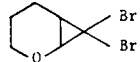

Chloromethyl phenylsulfide does not lead to phenylthio methyl magnesium derivative on reaction with Grignard reagents<sup>333</sup> whereas the bromo analogue and  $\alpha$ -bromo-n-alkylphenylsulfides (Table VIII B) produce the corresponding carbanions in good yield.<sup>4,219</sup> Increasing the substitution around the expected carbanionic center usually decreases the ease of carbanion synthesis: 2-phenylthiopropene (50%) instead of 2-lithio-2-phenylthio propane is formed when 2-bromo-phenylthiopropene || is reached with n-BuLi in THF at  $-78^\circ$  or  $-110^\circ$ .<sup>74</sup>

|| This derivative loses readily HBr on standing at 20 for sometime and produces 2-phenylthiopropene.



Table VIII B.



						Ref.
a	$(\text{CH}_3)_3\text{SiCH}_2\text{Br}$	BuLi, ether	-23	1	60	368
b	$(\text{C}_6\text{H}_5)_3\text{SiCH}_2\text{Br}$	BuLi, ether	-78	0,3	78	368
c	$(\text{C}_6\text{H}_5)_3\text{SiCH}_2\text{Cl}$	BuLi, ether	—	—	very low yield	368
d	$(\text{C}_6\text{H}_5)_3\text{SiCH}(\text{Br})\text{CH}_3$	BuLi, ether	-78	0,5	24	368
e	$\text{C}_6\text{H}_5\text{SCH}_2\text{Br}$	BuLi, THF	-78	0,02	55	74
f	$\text{C}_6\text{H}_5\text{SCH}_2\text{Cl}$	$\left\{ \begin{array}{l} \text{tC}_4\text{H}_9\text{MgBr, ether} \\ \text{eC}_6\text{H}_{11}\text{MgBr, ether} \end{array} \right.$			00	333
g	$\text{C}_6\text{H}_5\text{S}-\text{CH}(\text{Br})\text{C}_6\text{H}_{13}$		BuLi, THF	-78	0,02	67
h		BuLi, THF	90, -78	0,3,2	92	438
i	$(\text{C}_6\text{H}_5)_3\text{GeCH}_2\text{Br}$	BuLi, THF	+20	0,1	90	368
j	$\text{C}_6\text{H}_5\text{SeCH}_2\text{Br}$	BuLi, THF	-78	0,05	75	439
k	$\text{C}_6\text{H}_5\text{SeCH}(\text{Br})\text{CH}_3$	BuLi, THF	-78	0,05	62	439
l	$\text{C}_6\text{H}_5\text{Se}-\text{C}(\text{Br})(\text{CH}_3)_2$	BuLi, THF	-78	0,05	62	439
m	$(\text{C}_6\text{H}_5)_3\text{SnCH}_2\text{I}$	BuLi, ether	-50	0,1	98	440
n	$(\text{C}_6\text{H}_5)_3\text{PbCH}_2\text{I}$	BuLi, ether	-50	—	58	274
o	$\text{ClCH}_2\text{Br}^+$	BuLi, THF	-110	0,1	75	441
p	$\text{BrCH}_2\text{Br}^+$	BuLi, THF	-78	0,25	20	441
q	$\text{BrCH}(\text{Br})\text{CH}_3^+$	BuLi, THF	-78	1	95	236
r	$\text{Br}-\text{C}(\text{Br})(\text{CH}_3)_2^+$	BuLi, THF	-78	1	50	236
+ unstable, must be prepared in situ						
s		$\text{CH}_3\text{Li}$ (Trapp mixture)	-110	—	70	259
t		$\text{CH}_3\text{Li}$ , Ether	-80	—	95	442
u		BuLi, THF $\text{iC}_3\text{H}_7\text{MgCl}$ , THF	-108 -103	— —	76 74	438b, 443a 443a, c

Halogen-metal exchange was successfully used for the synthesis of  $\alpha$ -halogenoalkyl-lithiums.<sup>33\*-35\*, 236, 259, 438, 441-444</sup> However, the reaction must be performed in several instances in the presence of an electrophile to trap the carbanion *in situ* and avoid its decomposition to carbene.

### IIB3 Group IVa belonging heteroatom carbon-bond cleavage (transmetallation reaction)

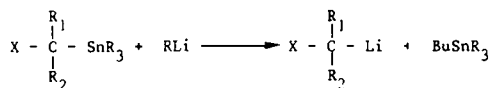
The cleavage of the C-Si, C-Ge and C-Pb bond has been only scarcely described in the literature<sup>1\*</sup> whereas several reports from Seyferth deals with the cleavage of the C-Sn bond.<sup>1\*</sup>

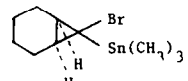
The C-Si bond cleavage in bis(trimethylsilyl) methane by sodium methylate was once described<sup>402</sup>††† (Table IXA) and C-Pb bond cleavage by n-BuLi was recently used<sup>274</sup> for the high yield synthesis of triphenylplumbyl and triphenylgermyl-methylolithiums (Table IXA).

				Ref.
$(\text{CH}_3)_3\text{Si}-\text{CH}_2-\text{Si}(\text{CH}_3)_3$	$\xrightarrow[\text{HIPT}]{\text{NaOCH}_3}$	$(\text{CH}_3)_3\text{Si}-\text{CH}_2\text{Na}$	53%	4b*, 402
$(\text{C}_6\text{H}_5)_3\text{Ge}-\text{CH}_2-\text{Ge}(\text{C}_6\text{H}_5)_3$	$\xrightarrow{\text{RLi}}$	$\text{C}_6\text{H}_5\text{Ge}-\text{CH}_2\text{Li}$	0%	4b*
$(\text{C}_6\text{H}_5)_3-\text{Pb}-\text{CH}_2-\text{Pb}(\text{C}_6\text{H}_5)_3$	$\xrightarrow[\text{THF, -70}^\circ]{\text{C}_6\text{H}_5\text{Li}}$	$(\text{C}_6\text{H}_5)_3\text{Pb}-\text{CH}_2\text{Li}$	100%	4b*, 274
$(\text{C}_6\text{H}_5)_3\text{Ge}-\text{CH}_2-\text{Pb}(\text{C}_6\text{H}_5)_3$	$\xrightarrow{\text{C}_6\text{H}_5\text{Li}}$	$(\text{C}_6\text{H}_5)_3\text{Ge}-\text{CH}_2\text{Li}$	87%	4b*, 274

The C-Sn bond cleavage by n-BuLi allows the synthesis of a large variety of  $\alpha$ -heterosubstituted methylolithiums (Table IXB) but surprisingly only few alkylolithiums bearing one or two alkylgroups on the carbanionic center have been prepared by this route (dialkylamino)methylolithium unavailable by other routes is quite quantitatively obtained from  $\alpha$ -aminostannane and n-BuLi<sup>445,446</sup> (Table IXB).  $\alpha$ -alkoxyalkylolithiums<sup>447,448</sup> (Table IXB, d-i) even bearing one alkylgroup on the

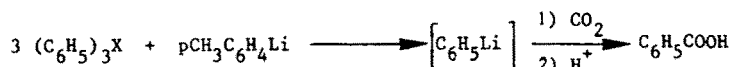
Table IXB.



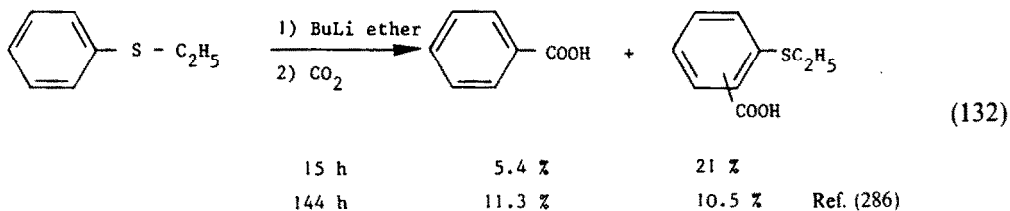
		Conditions	°C	Time (hr)	Yield(%)	REF.	
a	$(\text{CH}_3)_2\text{N}-\text{CH}_2-\text{SnBu}_3$	BuLi	Hexane-TMEDA	20	1	86	445
b	$(\text{CH}_3)_2\text{N}-\text{CH}_2-\text{SnBu}_3$	"	Hexane	0	0,01	73	446
c	$(\text{C}_6\text{H}_5)_2\text{NCH}_2-\text{SnBu}_3$	"	THF-hexane	0	1,5	83	446
d	$\text{CH}_3\text{O}-\text{CH}_2-\text{SnBu}_3$	"	Hexane	—	—	86	447
e	$(\text{CH}_3\text{O}-\text{CH}_2)_4\text{Sn}$	"	ether or THF	—	—	70	447
f	$\text{CH}_3\text{O}-\underset{\text{C}_6\text{H}_{13}}{\text{CH}}-\text{SnBu}_3$	"	THF	-78	0,1	98	448
g	$\text{C}_2\text{H}_5\text{O}-\underset{\text{CH}_3}{\text{CH}}-\text{O}-\text{CH}_2-\text{SnBu}_3$	"	THF	-78	0,1	94	448
h	$\text{C}_2\text{H}_5\text{O}-\underset{\text{CH}_3}{\text{CH}}-\text{O}-\underset{\text{C}_6\text{H}_{13}}{\text{CH}}-\text{SnBu}_3$	"	THF	-78	0,1	81	448
i	$\text{C}_2\text{H}_5\text{O}-\underset{\text{CH}_3}{\text{CH}}-\text{O}-\text{C}(\text{C}_6\text{H}_{11})_2-\text{SnBu}_3$	"	THF	-78	0,1	00	448
j	$\text{HO}-\text{CH}_2-\text{SnBu}_3$	"	Pentane	+20	6	62	449
k	$\text{Me}_3\text{Si}-\text{CH}_2-\text{SnBu}_3$	"	THF	+20	24	0	452
l		"	THF-TMEDA	+20	24	25	452
m	$(\text{C}_6\text{H}_5)_3\text{Sn}-\text{CH}_2-\text{Sn}(\text{C}_6\text{H}_5)_3$	$\text{C}_6\text{H}_5\text{Li}$	—	—	—	36	4b*
n	$\text{CH}_3\text{S}-\text{CH}_2-\text{SnBu}_3$	BuLi	Hexane	—	—	85	450
o	$p\text{CH}_3\text{C}_6\text{H}_4\text{S}-\text{CH}_2-\text{Sn}(\text{C}_6\text{H}_5)_3$	"	Hexane	70	1,5	50	451
p		"	THF	-95	3	60	443c

††† The cleavage of the C-Si bond in triiodo-(trimethylsilyl)methane by dichloromethyl lithium was also described (12% yield).<sup>424</sup>

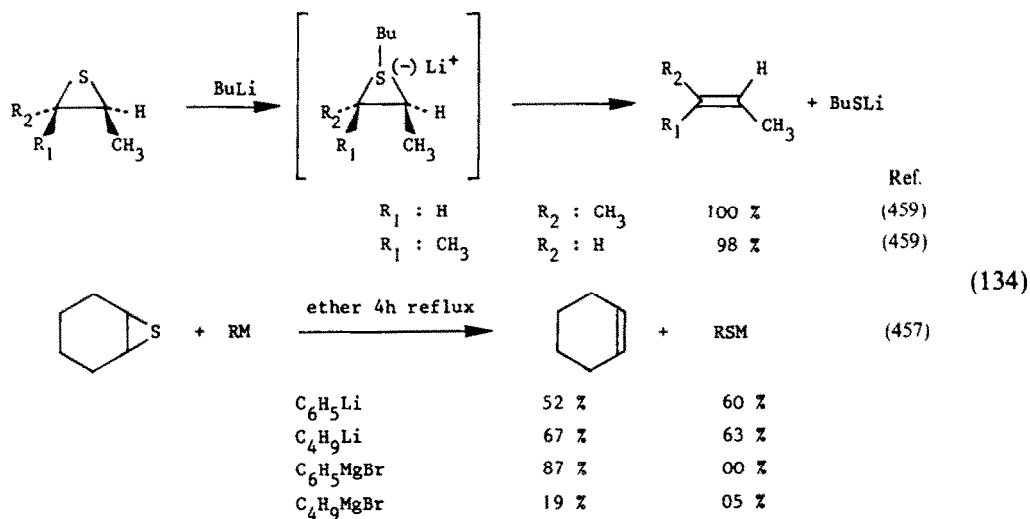
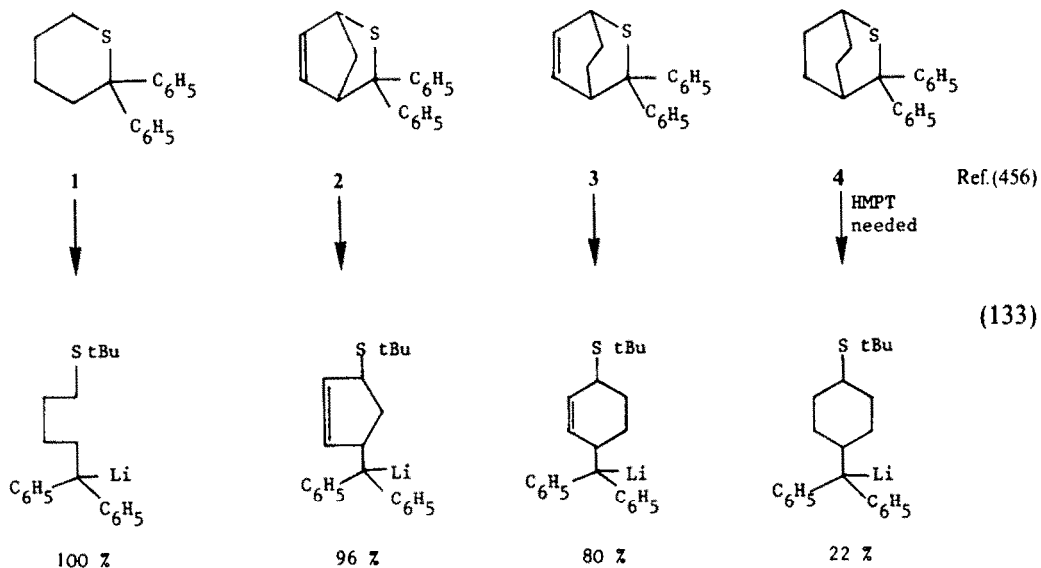


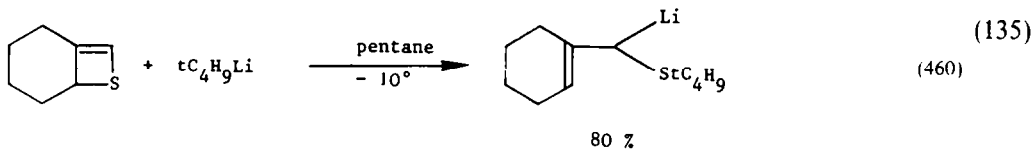
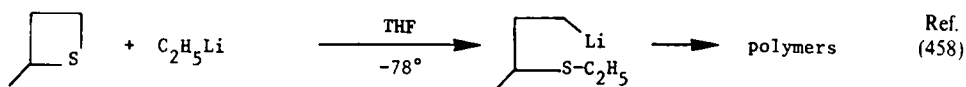


X:	N	P	As	Sb	Bi	
Yield in benzoic acid						(131)
a) after 4 days	0	1.4	1	92.3	94.1	
b) after 6 weeks	0	21.8	7.2	94.8	95.3	Ref. (454)



Reaction of *t*BuLi - THF - TMEDA (-10°, 1 hr).

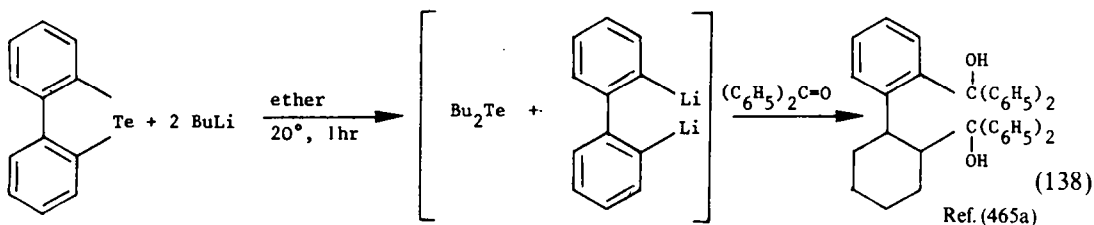
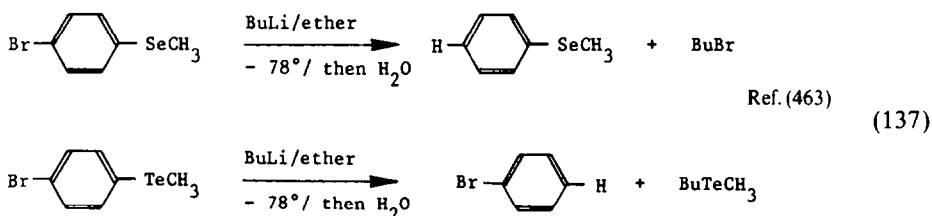




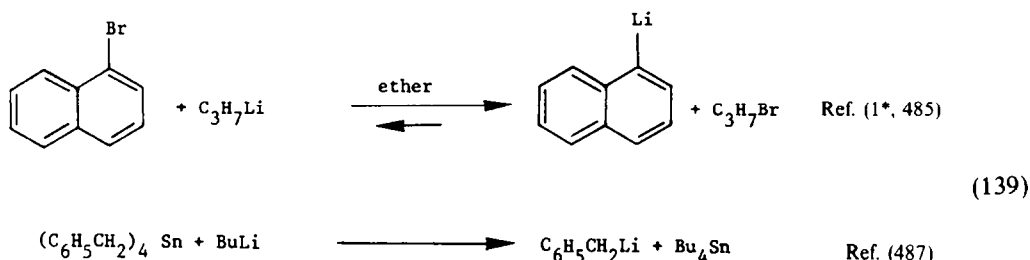
		$\xrightarrow{\text{RM}}$	[	$\xrightarrow{\text{E}}$	$\text{R}_1\text{E} + \text{RE}$	Ref.
a	$\text{CH}_3\text{SeCH}_3$	BuLi/THF 20°	$\text{C}_6\text{H}_5\text{CH} = \text{O}$		$\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{-OH}$ (32%) $\text{C}_6\text{H}_5\text{CHOH}(\text{C}_6\text{H}_5)$ (44%)	(229)
b	$\text{C}_6\text{H}_5\text{SeCH}_3$	BuLi/THF 20°	$\text{C}_6\text{H}_5\text{CH} = \text{O}$		$\text{C}_6\text{H}_5\text{CH}(\text{C}_6\text{H}_5)\text{-OH}$ (93 %)	(229)
c	$\text{C}_6\text{H}_5\text{SeCH}_3$	BuLi/ether-reflux	$\text{CO}_2$		$\text{C}_6\text{H}_5\text{COOH}$ (29 %)	(425)
d	$\text{C}_6\text{H}_5\text{SeCH}_3$	AmylNa/hexane 20°, 4h	$\text{CO}_2$		$\text{C}_6\text{H}_5\text{COOH}$ (25 %)	(425)
e	$\text{C}_6\text{H}_5\text{SeC}_6\text{H}_5$	BuLi/THF 20°	$\text{C}_6\text{H}_5\text{CH} = \text{O}$		$\text{C}_6\text{H}_5\text{-CH}(\text{C}_6\text{H}_5)\text{-OH}$ (72 %)	(229)
f	$\text{C}_6\text{H}_5\text{SeCH}_2\text{C}_6\text{H}_5$	BuLi/THF 20°	$\text{C}_6\text{H}_5\text{CH} = \text{O}$		$\text{C}_6\text{H}_5\text{CH}(\text{CH}_2\text{C}_6\text{H}_5)\text{-OH}$ (75 %)	(461, 229)
g	$\text{C}_6\text{H}_5\text{Se-CH=CH-CH}_3$	BuLi/THF 20°	$\text{C}_6\text{H}_5\text{CH} = \text{O}$		$\text{C}_6\text{H}_5\text{-CH}(\text{C}_6\text{H}_5)\text{-OH}$ (60 %)	(229)
h	$\text{C}_6\text{H}_5\text{Se-CH=CH}_2$	BuLi/THF -78°	$\text{C}_6\text{H}_{13}\text{CH} = \text{O}$		$\text{C}_6\text{H}_5\text{CH}(\text{C}_6\text{H}_{13})\text{-OH}$ (68%)	(136, 233)
i	$\text{C}_6\text{H}_5\text{SeCH}_3$	BuLi-TMEDA Hexane <sup>+</sup>			$\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{-C}_6\text{H}_5$ ++	(186b)

+ There is a difference between the text in which THF seems to be used as cosolvent and the experimental data.

++ Metalations occurs at 0°C in this medium in 40% yield but not at -78°. There is no mention of the remaining 60% (recovery of unchanged methyl phenyl selenide or cleavage of the C-Se bond).



The reactions described in Eqs. (130–138) can be related to two well-known reactions. On one side, to the halogen metal exchange<sup>1\*,485</sup> (in which the heteroatom belongs to Group VIIa in the Periodic Table) (Chapter IIB2) and on the other side the Group IVA-heteroatom-metal exchange<sup>1\*,487</sup> exemplified by the C–Sn bond cleavage (Chapter IIB3) (Eq. 139).<sup>487</sup>



Equation (137) shows<sup>463</sup> the different aptitude of C–H, C–Br, Se–CH<sub>3</sub>, Se–Aryl, Te–CH<sub>3</sub> and Te–Aryl bond to be cleaved by n-BuLi.

( $\alpha$ ) *The ease of the reaction depends on the nature of the heteroatom.*

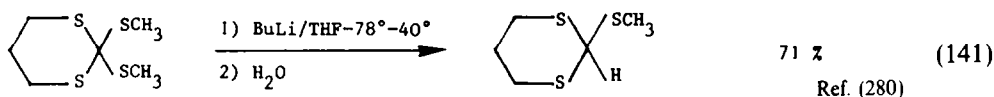
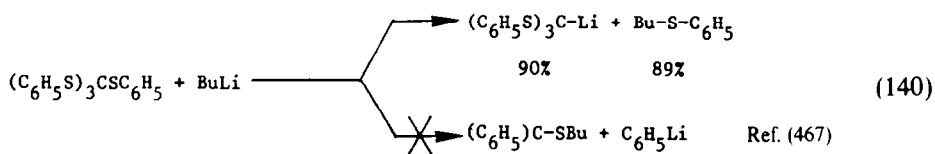
The reaction does not occur in the case of second row heteroatoms (nitrogen, oxygen) and the cleavage of the carbon-heteroatom bond is easiest by increasing the atomic number of the heteroatom in the same group (it is interesting to remember that the metallic character increases in the same direction); the data described by Wittig<sup>454</sup> (Eq. 131) clearly exemplify this tendency.

( $\beta$ ) *The reaction is highly enhanced if the heteroatom is part of a strained ring. || ||*

Alkylolithiums attack the S atom of thiiranes<sup>457–459,486</sup> (Eq. 134), thiacyclobutanes<sup>457,458</sup> and thiacyclobutene<sup>460</sup> (Eq. 135) destroying the heterocycle by cleavage of the C–S bond, whereas ethyl phenyl sulfide is cleaved in very low yield by n-BuLi (5.4 yield) under quite drastic conditions<sup>286</sup> (Eq. 132).

( $\gamma$ ) *The more stabilized is the expelled carbanion the easiest the reaction is.*

For example, whereas as already mentioned, ethyl and isopropylphenyl sulfides<sup>286</sup> (Eq. 132), thiacyclopentane<sup>458</sup> and thiacycloheptane<sup>458</sup> are inert toward alkylolithiums, thiophilic attack of t-BuLi (in THF–TMEDA) has been described<sup>456</sup> on 2,2-diphenyl thiacyclohexane (**1**, Eq. 133), 3,3-diphenyl-2-thia (2:2:1) bicyclo 5-heptene (**2**, Eq. 133), 3,3-diphenyl-2-thia (2:2:2) bicyclo 5-octene (**3**, Eq. 133) and 3,3-diphenyl-2-thio (2:2:2) bicyclooctane (**4**, Eq. 133). In all cases, the thiophilic attack is followed by the cleavage of the carbon-sulfur bond which produces the more stabilized of the two possible carbanions. It was also described that BuLi cleaves the C–S bond in tetrakis(phenylthio)methane<sup>467</sup> leading to tris(phenylthio)methylithium, free from phenyllithium arising from the cleavage of the other carbon sulfur bond (Eq. 140).



Similar cleavage was described when dithiomethyl-1,3-dithiane is reacted with BuLi<sup>280</sup> (Eq. 141).

This tendency to produce the best stabilized carbanion has been many times noticed. Thus alkylolithium selectively cleave the phenyl-heteroatom bond in diphenyl methyl phosphine<sup>267</sup> (Eq. 130), phenylselenides<sup>229,266,425</sup> (Eq. 136, entry b, c; d; e) and biphenyltelluride<sup>465</sup> (Eq. 138).

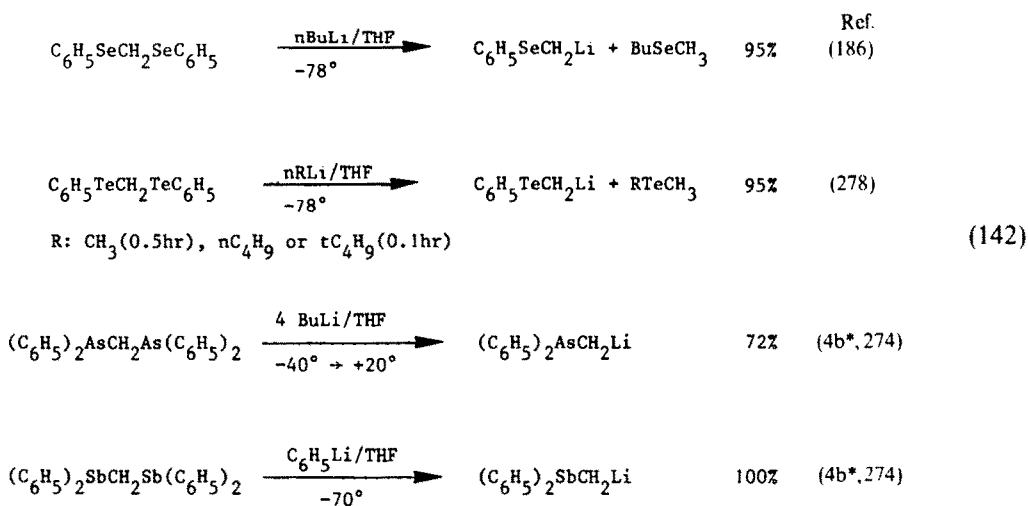
|||Strain around the P atom in phosphonium salts, favor the attack of alkyl and aryl lithium on the phosphorus at the expense of the metallation reaction.<sup>470,473,474</sup>

Otherwise *p*-tolyllithium reacts with triphenyl phosphine arsine, stibine and bismutine producing exclusively phenyllithium (trapped as benzoic acid after carbonation<sup>454</sup> (Eq. 131).

( $\delta$ ) *The cleavage reaction is highly influenced by the nature of the solvent.*

A too basic solvent enhances the competing metallation reaction, whereas no reaction occurs in solvents of low polarity. Usually THF seems to be the most valuable. For example diphenyl methylphosphine is inert toward BuLi in hexane or ether<sup>267</sup> but cleaved in 31% yield in THF (c/m: 1.7). Addition of complexing TMEDA increases the cleavage but also the metallation reaction which is relatively more enhanced<sup>267</sup> under these conditions (Eq. 130: compare a–b, c to d, f to g). Methyl phenylselenide is much more prone to cleavage reaction. This occurs in low yield in ether (29%, Eq. 136c) and quite quantitatively in THF<sup>229</sup> (90%, Eq. 136 b) but addition of TMEDA to the medium leads to 40% metallation,<sup>186</sup> which is not found under other conditions (Eq. 136i).

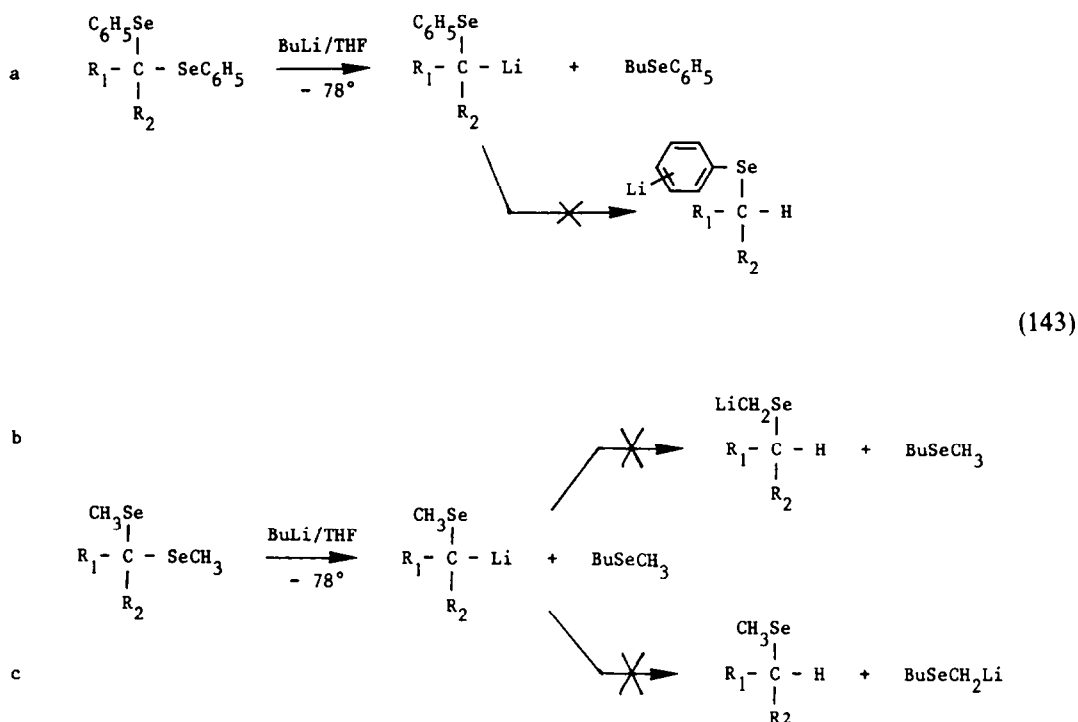
(b) *Use of carbon-heteroatom (belonging the Group V and VI) bond cleavage for  $\alpha$ -monohetero substituted carbanion synthesis.* The cleavage of the C–Se and C–Te bond respectively in bis(phenylseleno)methane and in its phenyltelluro analogue by *n*-BuLi was first described by Seebach.<sup>186, 278</sup> It allows the respective and quantitative formation of phenylseleno methylithium<sup>186</sup> and its telluro analogue<sup>278</sup> (Eq. 142). More recently Kauffman described<sup>274</sup> the synthesis of diphenylarsinomethylithium and its stibino analogue taking advantage of the cleavage C–As and C–Sb bond by *n*-BuLi in bis(diphenylarsino)methane and in bis(diphenylstibino)methane (Eq. 142).



( $\alpha$ ) *Synthesis of  $\alpha$ -selenoalkyllithiums.*

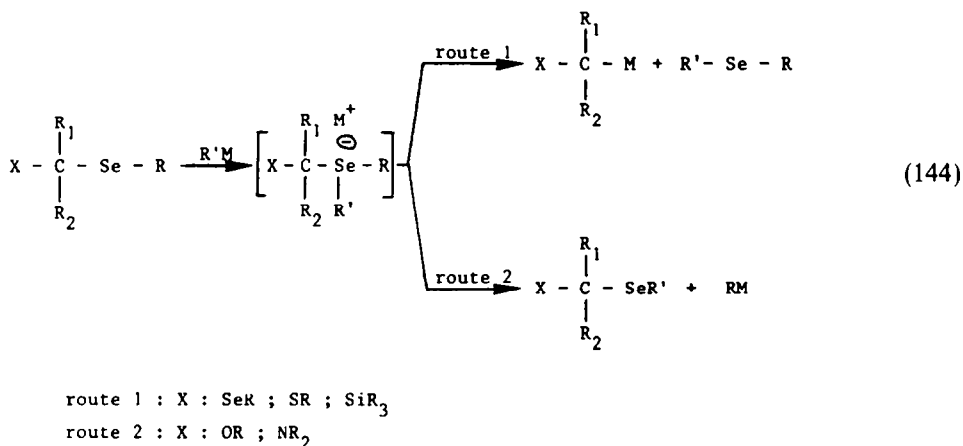
The cleavage of the C–Se bond by *n*-butyllithium in THF was further extended independently by us<sup>229</sup> and by Seebach<sup>220, 221</sup> to other phenylselenoacetals and by us to methylseleno analogues.<sup>76, 488, 509</sup> The reaction is easy and occurs quite instantaneously in this medium at  $-78^\circ$ . It allows the nearly quantitative synthesis of methyl- and phenylselenoalkyllithiums (the most widely used for synthetic purpose) even bearing one or two alkyl groups which can be part of a three,<sup>61, 488, 509a</sup> four,<sup>509b</sup> five<sup>232</sup> or six membered cycle (Eq. 160).<sup>76, 221, 497</sup>

Ethyl and heptylselenoacetals are also quantitatively cleaved<sup>489</sup> by *n*-BuLi in THF at  $-78^\circ$  whereas the reaction is very sluggish with selenoacetals derived from secalkylselenols<sup>489</sup> [ $\sim 40\%$  cleavage for  $CH_2(Se-iC_3H_7)_2$  or  $CH_3CH(Se-iC_3H_7)$ ;  $< 30\%$  for  $C_6H_{13}CH(Se-iC_3H_7)_2$ ,  $0\%$   $(CH_3)_2C(Se-iC_3H_7)_2$ ]. This disallows at present time the synthesis of  $\alpha$ -selenoalkyllithiums bearing a chiral center in  $\alpha'$  to the selenium atom. All these carbanions are stable for prolonged period at  $-78^\circ$  in THF. Interestingly under these conditions the phenylseleno derivatives do not epimerize to selenoaryllithium (Eq. 143a) and methylselenoalkyllithiums do not isomerise to the thermodynamically more stable alkylseleno methylithiums (Eq. 143b) nor react with the butyl methyl selenide resulting from the C–Se bond cleavage (Eq. 143c) (for detailed discussion see Chapter IIB4c).



The C-Se bond cleavage was successfully used for the synthesis of  $\alpha$ -hetero-substituted alkylolithiums others than the  $\alpha$ -selenoalkylolithiums just presented.

The success of the reaction is of course highly dependant on the nature of the heteroatomic moiety but also depends on the nature of the groups attached to the expected carbanionic center and to the selenium atom (Eq. 144).

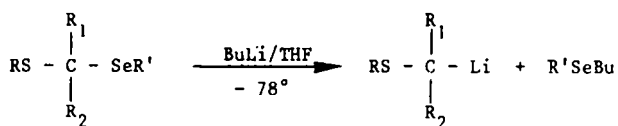


( $\beta$ ) Synthesis of  $\alpha$ -thioalkylolithiums.

The cleavage of the C-SeC<sub>6</sub>H<sub>5</sub><sup>52,73,74,219-221</sup> and C-SeCH<sub>3</sub><sup>52,74</sup> bond in mixed S, Se acetal and ketal by n-BuLi in THF is very easy, occurs instantaneously at -78° and allows the synthesis of  $\alpha$ -phenylthio<sup>52,73,74,219-221</sup> and  $\alpha$ -methylthio<sup>52,74,221</sup> bearing two hydrogens, one alkyl group or two alkyl groups on the carbanionic center (Eq. 145).

The selenium-metal exchange is exclusively observed with mixed acetal derived from aldehydes at the condition to avoid an excess of the mixed acetal which is further metallated by the  $\alpha$ -thioalkylolithium prepared.<sup>74</sup>





R	R <sub>1</sub>	R <sub>2</sub>	R'	yield %	Ref.
C <sub>6</sub> H <sub>5</sub>	H	H	C <sub>6</sub> H <sub>5</sub>	94	(73, 74) +
C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	98	(73, 74, 220)
C <sub>6</sub> H <sub>5</sub>	H	CH(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	96	(219)
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	95	(73, 74, 220, 221)
C <sub>6</sub> H <sub>5</sub>	CH <sub>2</sub> -(CH <sub>2</sub> ) <sub>3</sub> -CH <sub>2</sub>		C <sub>6</sub> H <sub>5</sub>	95	(220, 221)
C <sub>6</sub> H <sub>5</sub>	H	H	CH <sub>3</sub>	95	(74)
C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	95	(74)
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	95	(74)
CH <sub>3</sub>	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	95	(74)

(145)

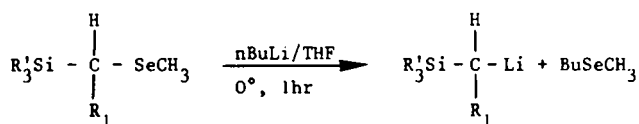
+ if large scale reaction is performed the selenoacetal must be added to nBuLi to avoid metallation reaction.

The competing metallation reaction<sup>74</sup> is particularly favoured in mixed selenoacetals derived from formaldehyde. It can be completely avoided in phenylthio, phenylseleno methane by adding the mixed selenoacetal to n-BuLi (THF, -78°). But mixture of metallated acetal and phenylthio methylithium are always formed from methylthio phenylseleno methane and n-BuLi (THF, -78°) whatever the experimental conditions used.<sup>74</sup>

( $\gamma$ ) *Synthesis of  $\alpha$ -silylalkyllithiums.*

The cleavage of the C-Se bond in  $\alpha$ -silyl selenides is not as easy<sup>47</sup> as in the cases just described (Chapter IIB4ba and IIB4bb).

In fact  $\alpha$ -silyl-methylselenides are inert to n-BuLi in THF at -78°. Raising the temperature at 0° allow the cleavage to occur:  $\alpha$ -silyl carbanions bearing a hydrogen or one alkyl group are formed in about 40% yield under these conditions<sup>47</sup> whereas those bearing two alkyl groups on the carbanionic center remain unknown<sup>47</sup> (Eq. 146).



R'	R <sub>1</sub>	yield in <u>2</u> (%)	ref
CH <sub>3</sub>	C <sub>6</sub> H <sub>13</sub>	50 %	(47)
C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	40 % +	(47)
C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>13</sub>	30 %	(47)

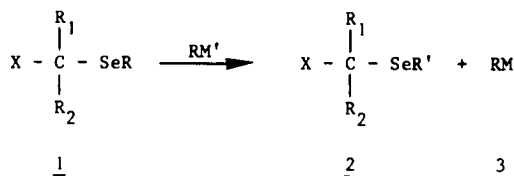
(146)

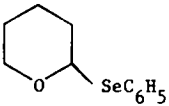
+ based on the yield of olefin formed after further reaction

$\alpha$ -Silyl phenylselenides behave differently than their methylseleno analogues when reacted with *n*-BuLi in THF. It was found<sup>47</sup> that they react at  $-78^\circ$  but the Se-phenyl bond is exclusively cleaved producing phenyllithium and  $\alpha$ -silylbutylselenides (Eq. 147).

( $\delta$ ) *Attempted synthesis of  $\alpha$ -alkoxy and  $\alpha$ -dialkylamino alkylolithiums.*

Similar behaviour was observed with  $\alpha$ -alkoxyselenides<sup>73,221</sup> and  $\alpha$ -aminoselenides<sup>73,221,232</sup> which are unresponsive towards alkylolithiums when a Me or a *t*-Bu group is attached to the Se atom (*n*-BuLi/THF; *t*-BuLi/THF or THF-TMEDA or THF-HMPT). Again changing the Me or *t*-Bu group by a phenyl group dramatically changes the course of the reaction, the alkylolithiums reacting rapidly onto the Se atom, even at  $-78^\circ$ , and producing phenyllithium instead of the desired  $\alpha$ -heterosubstituted carbanion (Eq. 147).



<u>1</u>	R'M	<u>2</u> (%)	<u>3</u> (%)	ref.
$(C_2H_5)_3SiCH-SeC_6H_5$ $C_6H_{13}$	<i>n</i> BuLi/THF ( $-78^\circ$ )	60	—	(47)
$CH_3O-CH_2SeC_6H_5$	<i>n</i> BuLi/THF	—	85	(73)
	<i>n</i> BuLi/THF	59	—	(221)
	<i>t</i> BuLi/THF	68.5	—	(221)
	<i>n</i> BuLi/THF	—	70	(232)
	<i>n</i> BuLi/THF	high	—	(221)
$(CH_3)_2N-CH_2SeC_6H_5$	<i>t</i> BuLi/THF ( $-78^\circ, -45^\circ$ )	48	—	(221)
	<i>n</i> BuLi/THF ( $-78^\circ$ )	several products	—	(232)

(c) *Further information on  $\alpha$ -selenoalkylolithiums.* Phenyl and methylselenoacetals and ketals have been the most widely used for synthetic purposes and thus have been the more widely studied. We will briefly present our preliminary observations in this field.

( $\alpha$ ) *Further information on the synthesis of  $\alpha$ -selenoalkylolithiums.*

Phenylselenoacetals behave differently than methylseleno analogues since they are generally more easily cleaved producing  $\alpha$ -selenoalkylolithiums and are more prone to undergo a competing hydrogen-metal exchange leading to  $\alpha$ -diselenoalkylolithiums.<sup>107,109,186</sup>

Although, all methyl- and phenylselenoacetals used were cleaved instantaneously and cleanly at  $-78^\circ$  by *n*-BuLi<sup>†</sup> in THF<sup>††</sup> (and behave similarly with *sec*- and *t*-BuLi in THF or ether).<sup>232</sup> The C-Se bond cleavage is not observed<sup>232</sup> with *n*- or *t*-BuLi in hydrocarbons and with *n*-BuLi in benzene or in alkylbenzenes. *n*-BuLi in ether is quite selective from  $-78^\circ$  to  $-43^\circ$  since it allows the quantitative cleavage of bis(phenylseleno)-methane, -ethane and 1,1-heptane at the exclusion of bis(phenylseleno)-2,2-alkanes and even in their presence.<sup>232</sup> Furthermore bis(methylseleno)methane and ethane produce the corresponding selenoalkylolithium in 70% yield under similar conditions.

<sup>†</sup> The reaction proceeds more and more slowly with ethyl, phenyl and methylolithiums in THF at  $-78^\circ$ .

<sup>††</sup> Under conditions described by Seebach<sup>186</sup> but on large scale reaction, the yield of phenylselenomethylolithium is quite low, due to metallation of unreacted bis-(phenylseleno)methane by the carbanion just formed. Reverse addition precludes the formation of bis-(phenylseleno)methylolithium (this metallation reaction does not occur with bis-(phenylseleno)heptane and will all methylseleno acetals).

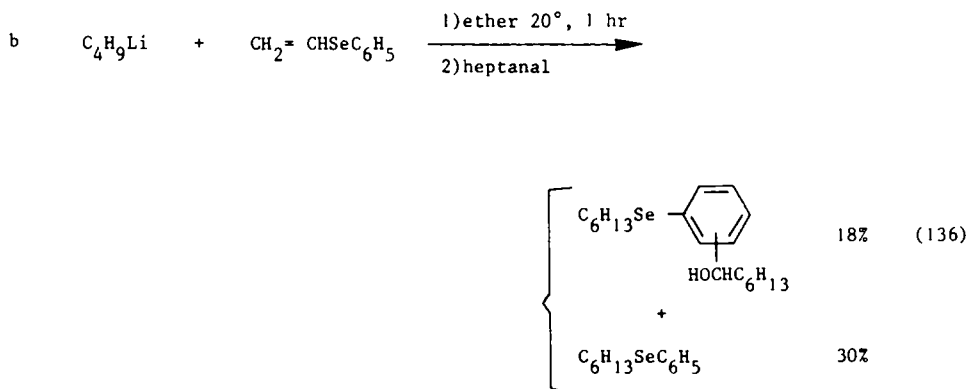
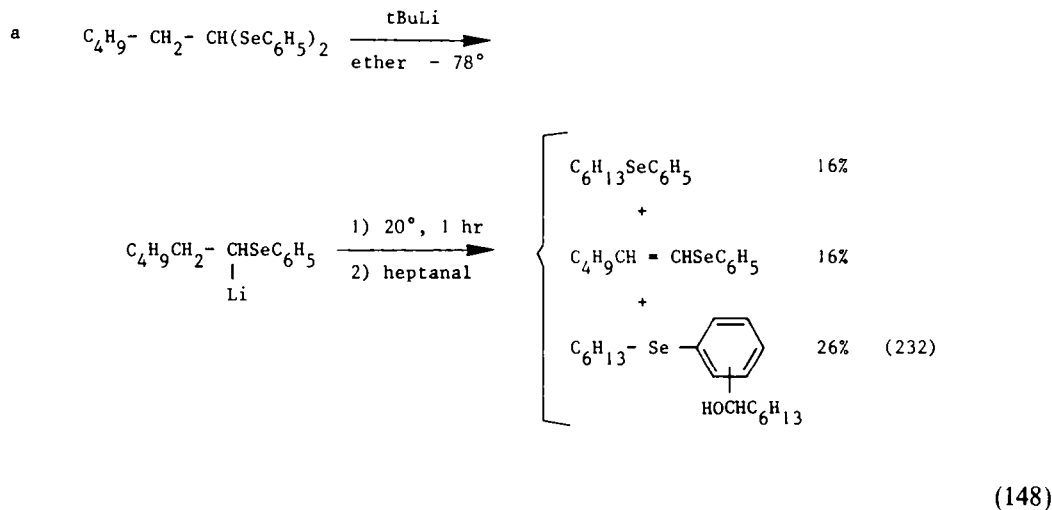
Both the cleavage and the metallation reactions were observed<sup>107,232</sup> in the case of phenylselenoacetals when the reaction are performed by *n*-BuLi in DME, THF-TMEDA or THF-HMPT.

The temperature has a great influence on the evolution of the reaction. In THF, and when *n*-BuLi is used, the cleavage of the C-Se bond occurs rapidly and selectively at  $-100$  to  $-78^\circ$  whereas metallation competes<sup>107</sup> in case of bis-(phenylseleno) methane **1** and ethane **2** when the reaction is performed at higher temperature (cleavage/metallation ratio: c/m for **1** ( $-100$  or  $-78^\circ$ ), 94/0: ( $-50^\circ$ ), 65/35: ( $0^\circ$ ), 60/40: ( $+25^\circ$ ), 45/65: **2** ( $-78^\circ$ ), 90/0: ( $-50^\circ$ ), 75/15: ( $-30^\circ$ ), 61/25).

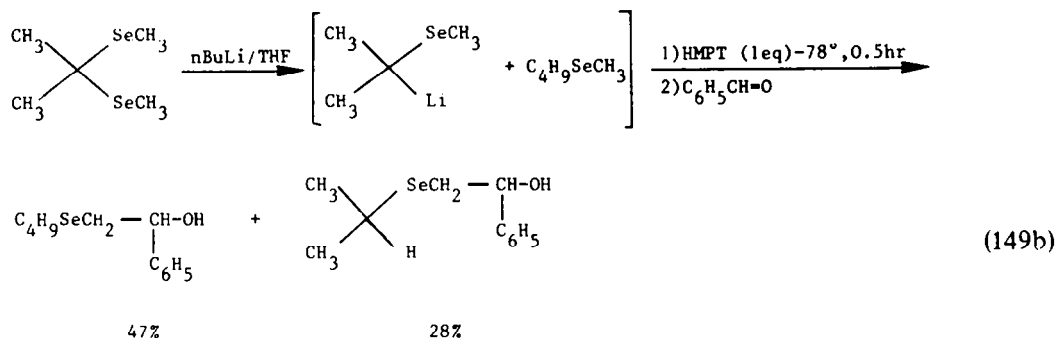
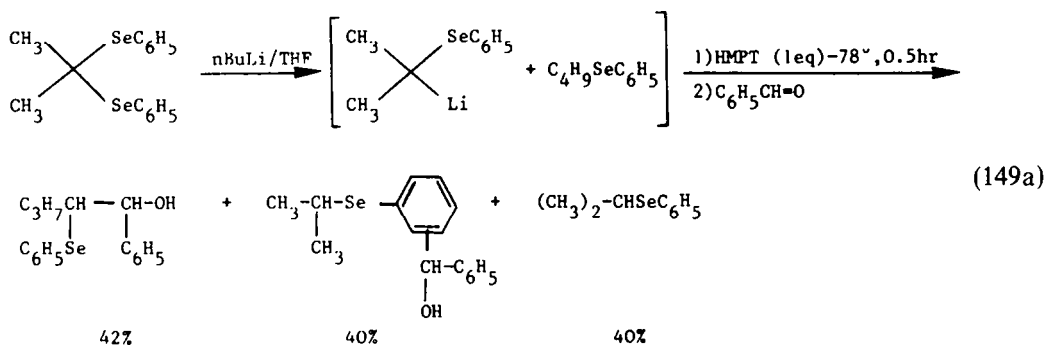
( $\beta$ ) *Further information on the stability of  $\alpha$ -selenoalkyllithiums.* The stability of  $\alpha$ -selenoalkyllithiums is an important question which will influence their synthetic usefulness.  $\alpha$ -Phenylseleno- and  $\alpha$ -methylseleno-alkyllithiums are stable for several hours (10 hr) at  $-78^\circ$  in THF. Except the special case of phenylselenomethylithium, which is stable in THF<sup>136,232</sup> even for 0.5 h at  $20^\circ$ , the other  $\alpha$ -selenoalkyllithiums decompose near to  $-20^\circ$ . The main degradative pathways include:

- the protonation reaction,
- the formation of vinyl selenides<sup>232</sup>
- the isomerisation of the ring metalated derivatives<sup>136,232</sup> which occurs with phenylselenoalkyllithiums in ether near to  $0^\circ$  (Eq. 148),
- the decomposition to lithioselenolate (and presumably to a carbene). For instances when epoxides and oxetanes are reacted with  $\alpha$ -selenoalkyllithiums a few percent of  $\beta$ -hydroxyselenides in the first case,  $\gamma$ -hydroxyselenides in the second one, are obtained along with the expected products (Eq. 106).

This side reaction is observed<sup>279</sup> in particularly high yield (40%) with methylselenomethylithium and even with phenylselenomethylithium which is quantitatively trapped with  $H_2O$  or benzaldehyde under similar conditions.<sup>186,279</sup> This side reaction can be prevented if a THF-HMPT solution of the epoxide is added to the  $\alpha$ -selenoalkyllithium in THF (Eq. 106).<sup>279</sup>



However,  $\alpha$ -selenoalkyllithiums are not particularly stable in presence of HMPT.<sup>279</sup> For example, 2-lithio-2-selenopropanes which are stable for prolonged period of time in THF at  $-78^\circ$ , rapidly metallate the butylmethylselenide or the butylphenylselenide present in the medium, when HMPT (1 eq.) is added<sup>279</sup> (Eq. 149) Transposition of the negative charge on the phenyl ring (in case of  $\alpha$ -phenylseleno alkylolithiums) and on the methylselenyl group (in case of  $\alpha$ -methylselenoalkyllithiums) are also observed under these conditions (Eq. 149).



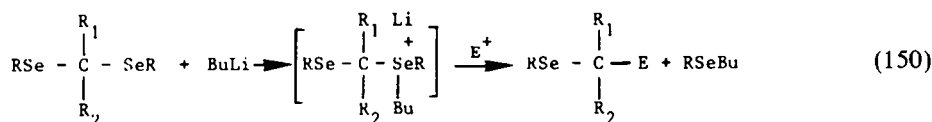
Finally only  $\alpha$ -selenocarbanions in which the counter ion is the lithium cation are known. Attempts to prepare copper derivatives by addition of  $\text{CuI}$ ,  $\text{C}_6\text{H}_5\text{SCu}$  or  $\text{CuI-Me}_2\text{S}$  to  $\alpha$ -selenoalkyllithiums in THF or ether were unsuccessful.<sup>238</sup>

We instead observed<sup>238</sup> the formation of an olefin resulting from an oxidative coupling (specific example will be presented in Chapter III, Eq. (160g), see also Eq. 95).

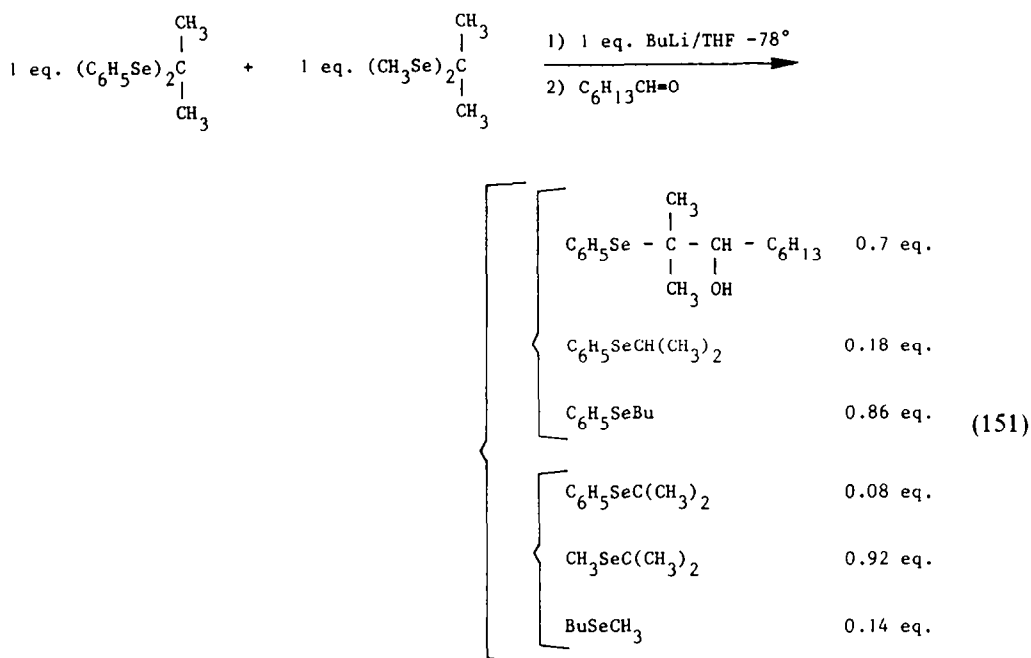
(v) *Special topics.*

The intimate mechanism of the formation of  $\alpha$ -selenoalkyllithiums from selenoacetals is under careful investigation in our laboratory using  $^{77}\text{Se}$  and  $^{13}\text{C}$ -NMR. Dr Dumont<sup>232</sup> found that a real  $\alpha$ -selenoalkyllithium is formed together with the selenide counterpart in THF at  $-78^\circ$  [e.i.  $^{77}\text{Se}$  NMR [( $\text{CH}_3$ )<sub>2</sub>Se as internal stand]  $\text{MeSe Bu}$ : +80.57,  $\text{C}_6\text{H}_5\text{Se Bu}$ : +287,  $\text{CH}_3\text{SeCH}_2\text{Li}$ : +61.43,  $\text{C}_6\text{H}_5\text{SeCH}_2\text{Li}$ : +279,  $\text{CH}_3\text{SeCHLi}$ : +100.57,  $\text{CH}_3\text{SeCLi}$ : +168 ppm] at the exclusion of a ate complex

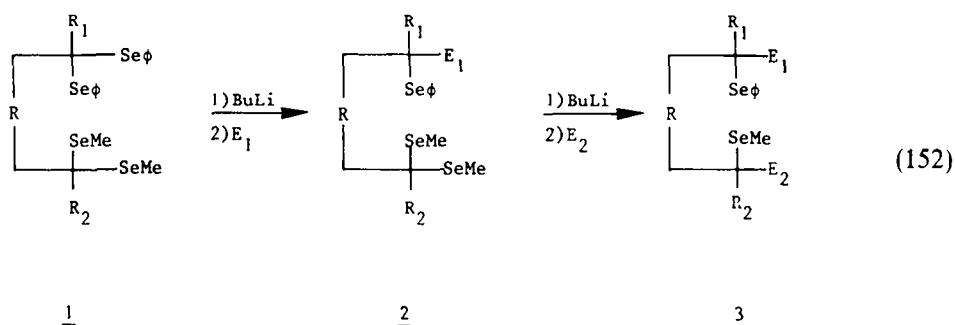
(Eq. 150) which can be formed intermediary but which is not observed under our conditions.



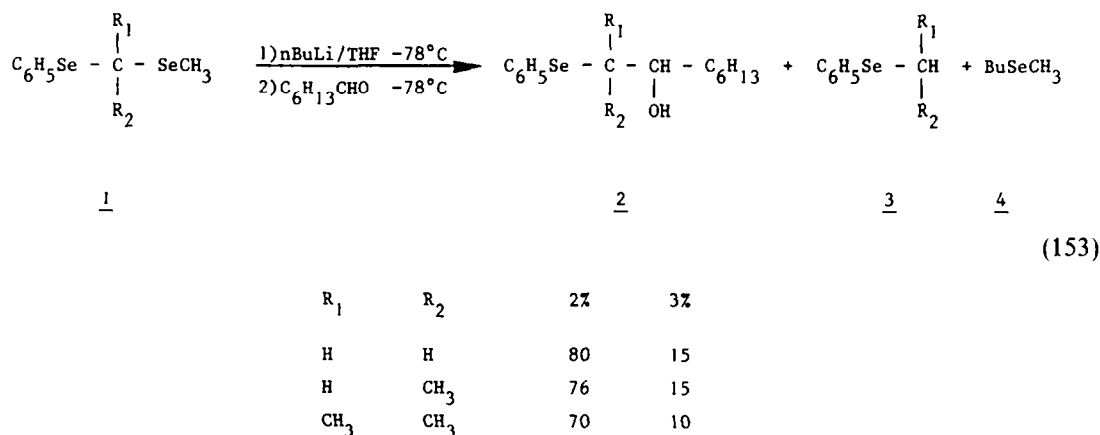
During the course of our research we had the opportunity to react a one to one mixture of phenylseleno and methylselenoacetals with only one equivalent n-BuLi (THF,  $-78^\circ$ ); we observed<sup>232</sup> the selective formation of phenylselenoalkyllithiums, the methylselenoacetals being recovered in high yield after the reaction (Eq. 151).



The observed selectivity would be valuable in organic synthesis as shown in Eq. (152). The methylselenoacetal group playing sequentially the role of a protecting group ( $1 \rightarrow 2$ ) or a reactive group ( $2 \rightarrow 3$ ).



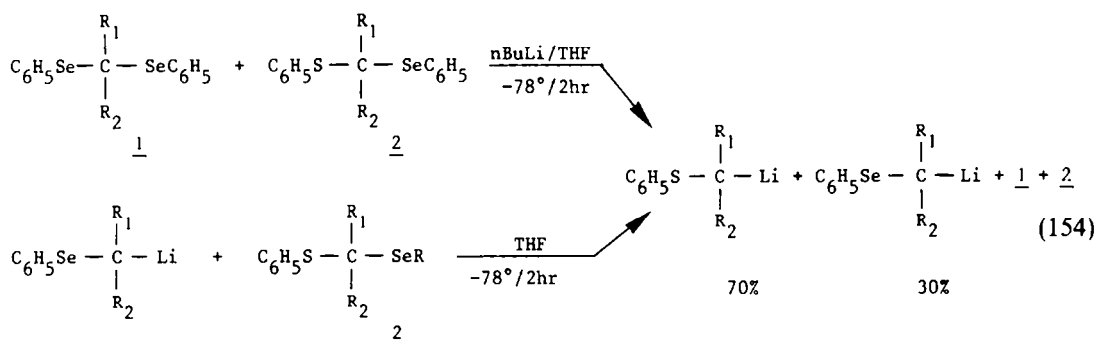
Another interesting selectivity was found: when mixed phenylseleno, methylseleno acetals are reacted with BuLi in THF ( $-78^\circ$ ), the carbon-methylseleno bond is the only one cleaved producing exclusively the  $\alpha$ -phenylselenoalkyllithiums<sup>232</sup> (no BuSeCH<sub>3</sub> found) (Eq. 153).



We finally found<sup>232</sup> that methylselenoalkyllithiums cleave the carbon-phenylseleno bond of the corresponding phenylseleno acetals producing thus phenylselenoalkyllithiums (Eq. 64).

All these results (Eq. 64, 151–153) including the highest reactivity toward *n*-BuLi of phenylselenoacetals compared to the methylseleno-analogues seems to agree with the hypothesis that the driving force of these transformations is the formation of the more stabilized carbanion. Much work is however needed to confirm this hypothesis.

Closely related to these observations is the formation of 2-phenylthio-2-lithio propane (70% after 2 hr) from 2-phenylseleno-2-lithio propane and 2-phenylthio-2-phenylseleno propane (THF:  $-78^\circ$ )<sup>232</sup> (Eq. 154). Similar results are obtained when a one to one mixture of 2-thiophenyl-2-phenylseleno propane and 2,2-bis-(phenylseleno) propane is reacted with only one equivalent of *n*-BuLi (THF,  $-78^\circ$ , 2 hr).<sup>232</sup>



These results can be explained by the difference of stabilization of the two carbanionic species respectively by the phenylseleno and the phenylthio moieties. If it is the case, the phenylthio group should stabilize the carbanionic center a little bit than the phenylseleno group (in THF) and this should be contradictory to Lehn calculations<sup>217</sup> (in gas phase).

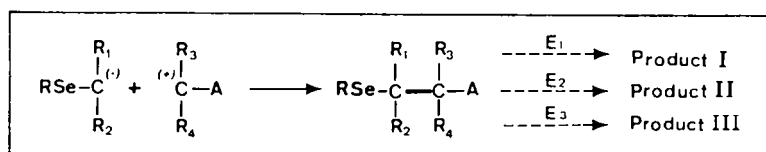
## CHAPTER III

 $\alpha$ -SELENOALKYLLITHIUMS IN ORGANIC SYNTHESIS

$\alpha$ -Seleno alkyllithiums are valuable building blocks in organic synthesis. This is due to their great availability (two steps from aldehydes or ketones, see below); the generality of their formation (even the dialkyl substituted ones are quantitatively prepared); their great stability at  $-78^\circ$  and last but not least to their high nucleophilicity (see below) which allow a new carbon-carbon bond formation when reacted with electrophilic carbon.

The resulting product is generally a stable selenide, functionalized or not, in which the selenyl moiety can be used as a "latent functionality". This can be selectively activated producing a large variety of different products when different reagent are used.

These proposals which are schematized in Eq. (155) will be discussed sequentially in this chapter.



(155)

GENERAL AVAILABILITY	HIGH NUCLEOPHILICITY LEADING TO HIGH YIELD C-C BOND FORMATION	SELECTIVE ACTIVATION LEADING SPECIFICALLY TO DIFFERENT PRODUCTS. P WITH DIFFERENT REAGENTS. E
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III A AVAILABILITY OF  $\alpha$ -SELENOALKYLLITHIUMS FOR SYNTHETIC PURPOSES

The best route§§§§ to  $\alpha$ -selenoalkyllithiums is the cleavage by alkyllithiums of the C-Se bond in selenoacetals.<sup>61, 76, 186, 220, 221, 229, 238, 488</sup> This is usually performed by *n*-BuLi in THF at  $-78^\circ$  for 0.3 hr. In some cases in which further reaction requires temperature higher than  $-78^\circ$  ( $-78^\circ$  to  $-30^\circ$ ) THF must be replaced by ether<sup>61, 238</sup> much less prone to metallation reaction. This reaction requires, as already mentioned the use of *sec* or *t*-BuLi in place of *n*-BuLi to occur.

## III A1 Synthesis of selenoacetals and ketals without concomittant C-C bond formation

(a) Bisselenomethanes are usually prepared from sodium or potassium selenolates and diiodo<sup>76, 186</sup> or dibromo<sup>230</sup> methane in alcoholic solvent (eqn 156).

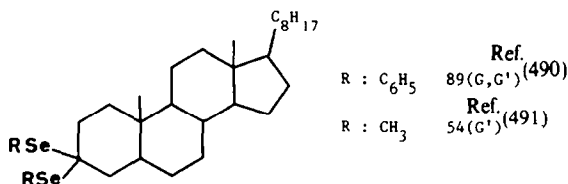
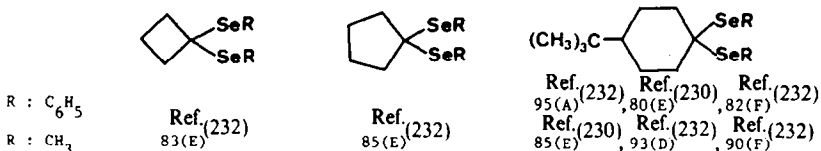
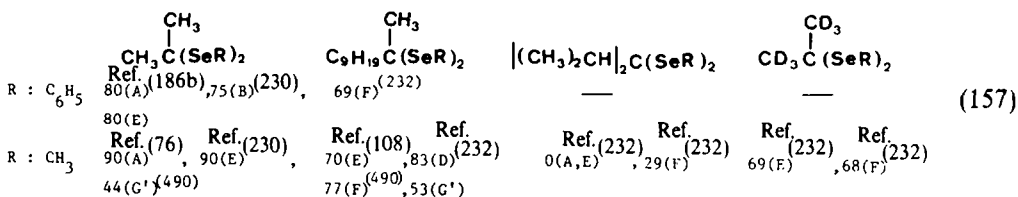
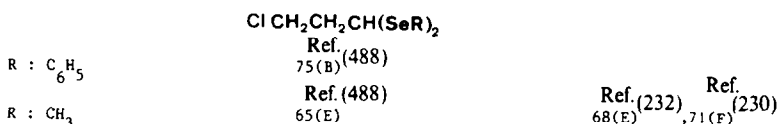
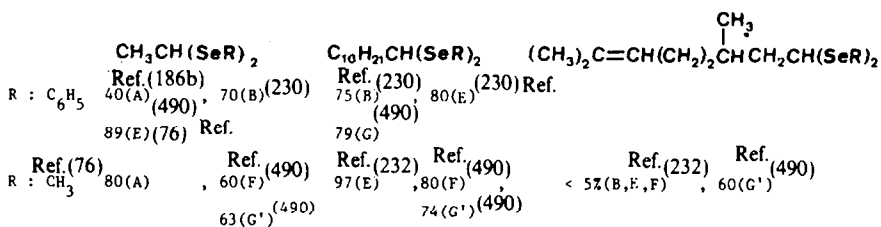
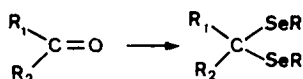


R	M	X	conditions	yield		
$C_6H_5$	Na	I	ROH/20°	95%	(186)	(156)
$CH_3$	K	I	ROH/20°	80%	(76)	
$C_6H_5$	Na	Br	$C_5H_{11}/*$	56%	(230 - 232)	

\* in presence of phase transfert catalyst

(b) Others selenoacetals and ketals are easily prepared from aldehydes and ketones (eqn 157).

§§§§ other routes disclosed are: the hydrogen-metal exchange (on methyl phenylselenide) the addition of organolithium to vinyl phenylselenide and the cleavage of the C-Br bond in  $\alpha$ -bromo selenides which allow the synthesis of all the  $\alpha$  diversely substituted phenyl selenoalkyllithiums (Chapter II).



(A) to (G') refers to the method used.

The selenyl moiety has been successfully introduced from selenols, trimethylsilylselenides or triselenoboranes. The former two methods require an acidic medium: HCl (A), <sup>76, 186, 488</sup> H<sub>2</sub>SO<sub>4</sub> (B), <sup>230</sup> BF<sub>3</sub>OEt<sub>2</sub> (C), <sup>232</sup> (TiCl<sub>4</sub> (D), <sup>232, 532</sup> ZnCl<sub>2</sub> (E))<sup>108, 230, 488, 532</sup> have been successfully used with selenols. HCl method (A) is not suitable in case of aldehydes when phenylselenol is used, <sup>230</sup> TiCl<sub>4</sub> (D) is the most powerful co-reagent since the reactions occur even at -50°, <sup>232, 532</sup> and ZnCl<sub>2</sub> (E) is one of the most suitable "catalyst" because it is not too acid, it is easy to handle and usually allows the synthesis of the desired selenoacetals or ketals in high yield (65-95%) at room temperature and for short reaction time (2-6 hr).<sup>108, 532</sup>

Trimethylsilylselenides are inert towards carbonyl compounds in neutral media.<sup>230</sup> In presence of MgBr<sub>2</sub> or ZnCl<sub>2</sub>, they produce O-(trimethylsilyl)monoselenoacetals<sup>230, 533</sup> and require AlCl<sub>3</sub> (F)<sup>230, 490</sup> to lead to selenoacetals and ketals (60-90% yield). Method F proved particularly useful for the synthesis of methylseleno derivatives since the required reagent (Me<sub>3</sub>SiSeR-AlCl<sub>3</sub>) can be prepared in situ from dimethyldiselenide, lithium aluminium hydride and chlorotrimethylsilane in ether, stored for prolonged period in CHCl<sub>3</sub>, and aliquots can be directly added to the carbonyl compound.<sup>490</sup> These conditions avoid the use of volatile (35°) and bad smelling methylselenol.

Triselenoboranes are also valuable reagents. Trisphenylselenoborane introduced by Clive<sup>491a</sup> usually requires an acid catalyst (G) whereas we found<sup>490a</sup> that the methylseleno analogue, easily



prepared from  $\text{BF}_3\text{OEt}_2$ ,  $\text{CH}_3\text{SeSeCH}_3$  and  $\text{AlLiH}_4$  and carefully distilled ( $G'$ ) works fine without addition of acid especially in case of aldehydes and cyclanones.

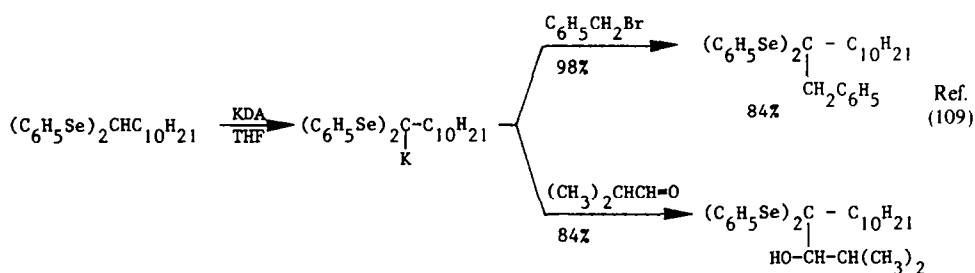
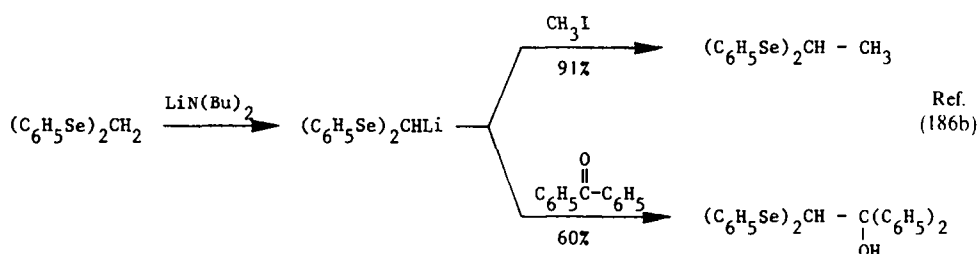
These last conditions are particularly suitable for the synthesis of selenoacetals from derivatives sensitive to acids such as citronellal (60% yield). However, all the methods presented (A–G) even the last one ( $G'$ ) cannot be used when an acetal or a ketal (derived from methanol) is already present in the molecule.<sup>2,32,491b</sup>

### IIIA2 Synthesis of selenoacetals with concomitant new carbon-carbon bond formation

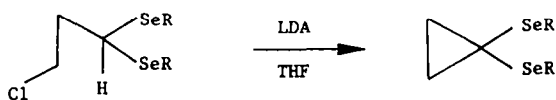
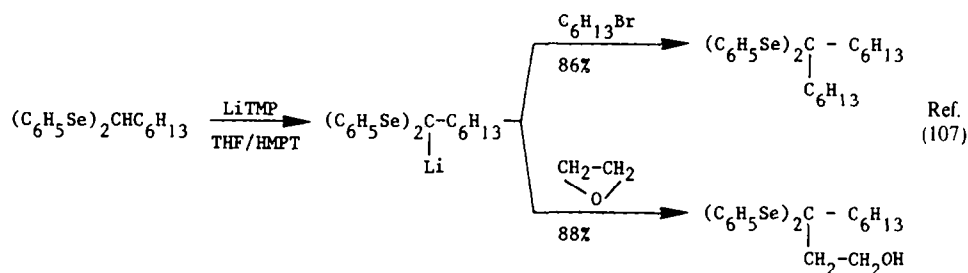
Selenoacetals and ketals can also be prepared from  $\alpha$ -diseleno alkylolithiums with concomitant carbon-carbon bond formation.

Diselenoalkyllithiums can be in turn prepared:

(a) by metallation of phenylseleno acetals (Eq. 158) which is performed by  $\text{LDBA}$ <sup>186</sup> or  $\text{LDA}$ <sup>107,488</sup> in THF ( $-78^\circ$ ) for bis-(phenylseleno)methane whereas higher homologues require stronger basic systems such as  $\text{LiTMP}$ <sup>107</sup> in THF-HMPT at  $-30^\circ$  or  $\text{KDA}$ <sup>109</sup> in THF at  $-78^\circ$ .



(158)



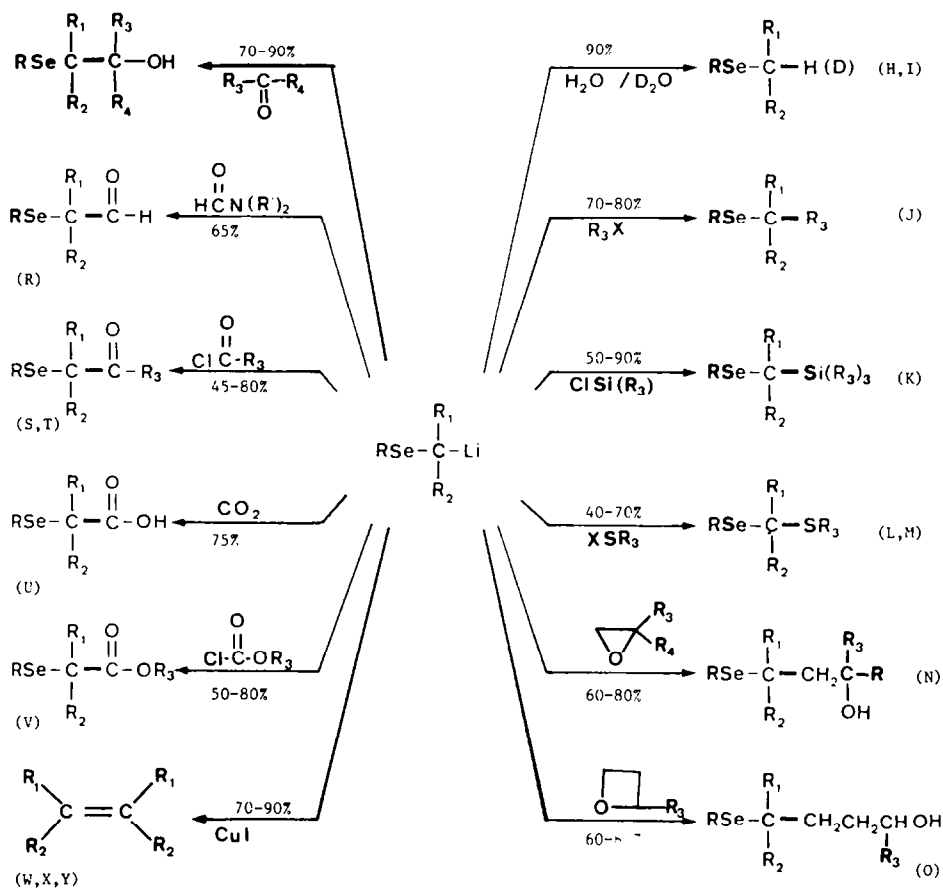
R :  $\text{CH}_3$  77% (488)

R :  $\text{C}_6\text{H}_5$  80% (488)

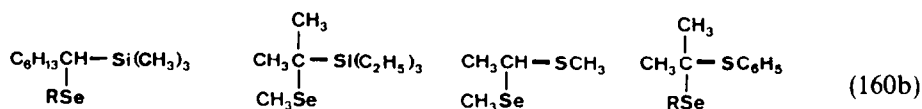
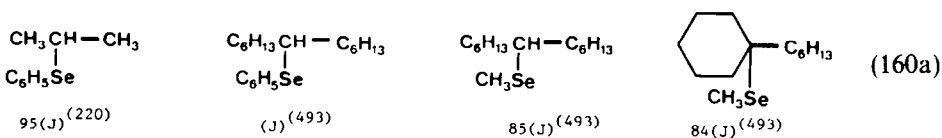
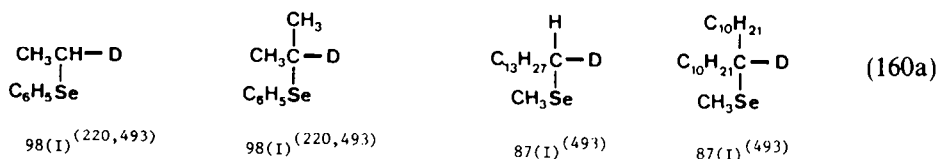
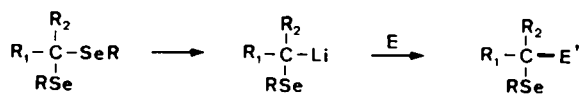


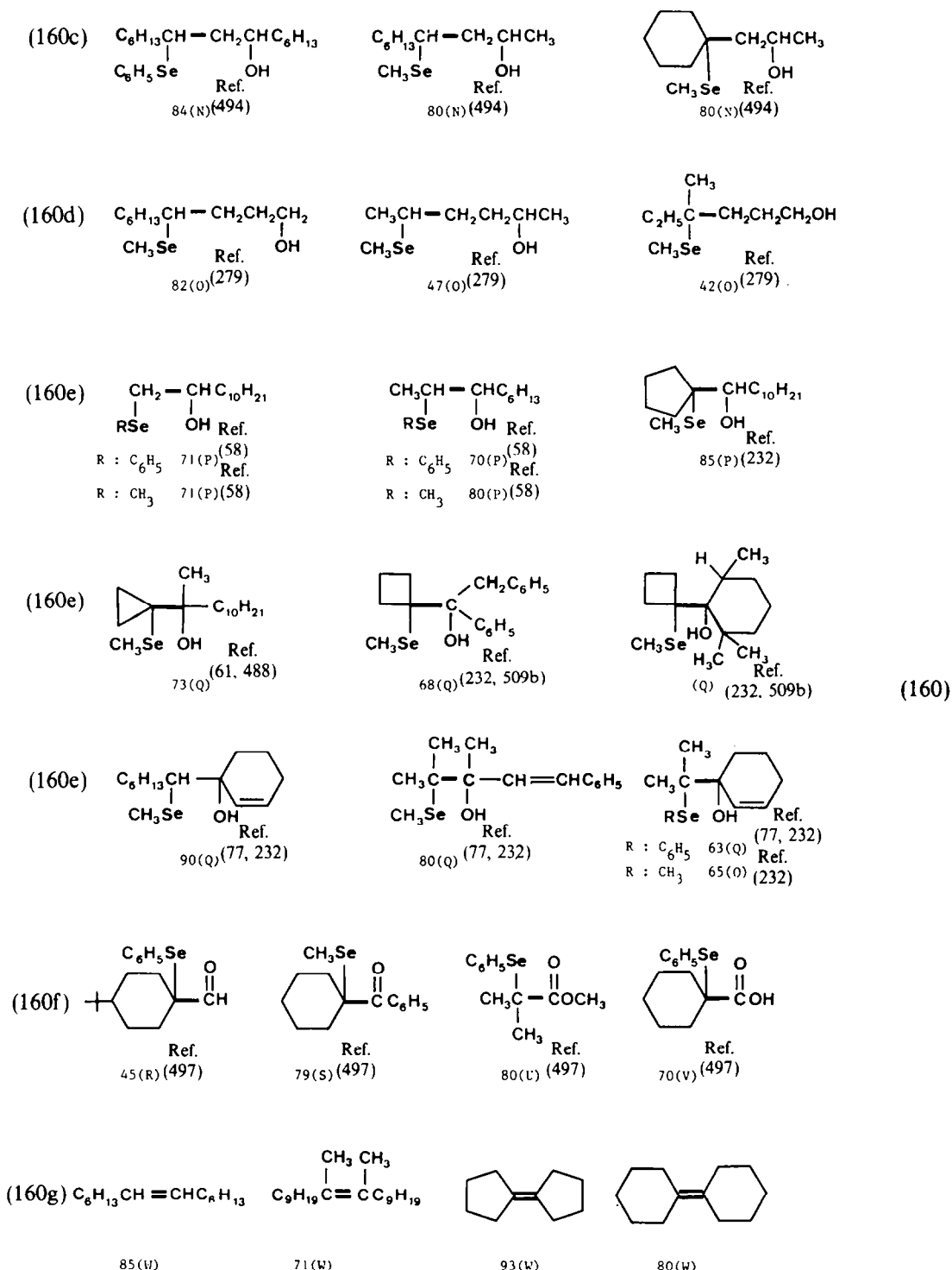
as 2,2,6,6-tetramethyl cyclohexanone<sup>76,496</sup> or highly enolisable ones such as deoxybenzoin<sup>58,60,61,76</sup> or the ones which combine the two particularities such as 2,2,6-trimethyl cyclohexanone<sup>496</sup> (Eq. 160e, Table X).

$\alpha$ -Enones which potentially possess ambident  $C_1/C_3$  reactivity react usually  $C_1$  with  $\alpha$ -selenoalkyllithiums producing thus  $\gamma,\delta$ -unsaturated  $\beta$ -hydroxyselenides in good yield<sup>77,232</sup> (Eq. 160e'): chalcone being the only example described on which both  $C_1$  and  $C_3$  attack of the carbanion is observed.<sup>77</sup>



(160)

R :  $C_6H_5$  51(K)<sup>(47)</sup>R :  $CH_3$  85(K)<sup>(47)</sup>(L)<sup>(74)</sup>



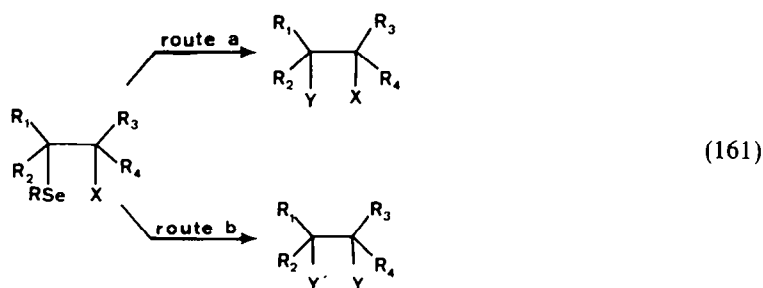
The experimental conditions used are particularly important for the success of the reactions presented. The highest yield of  $\beta$ -hydroxyselenides is usually found when the reaction is performed at the lowest temperature possible and in the less polar solvent. Both conditions lower their basicity and favor their nucleophilicity. For example, 2-lithio 2-methylseleno propane produces 80% yield of  $\beta$ -hydroxyselenide when reacted with 2,2,6-trimethyl cyclohexanone in ether<sup>496</sup> whereas the yield dramatically drops to 30% when the reaction is performed in THF.<sup>496</sup> Interestingly one of the two stereoisomers is mainly formed under each experimental conditions.<sup>496</sup> We also found<sup>232</sup> that the yield of 7-hydroxy-8-methylseleno tetradecane dramatically decreases when increasing percentage of

HMPT, known for its ability to prevent the assistance of the lithium cation, present during the reaction of 1-lithio-1-selenoheptane with heptanal.

### III C THE SELECTIVE ACTIVATION OF THE SELENYL MOIETY

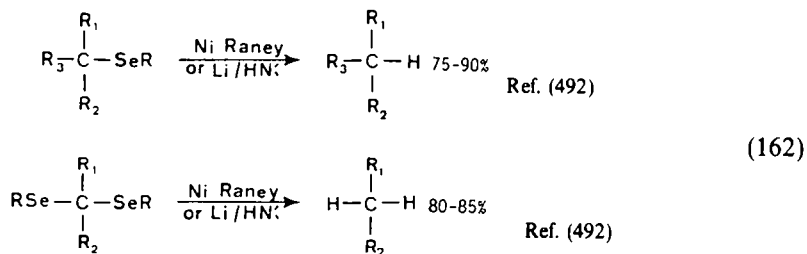
This last section is devoted to the selective removal of the selenium moiety in selenium containing molecules. Excellent reviews from Klayman–Gunther,<sup>30\*</sup> Sharpless,<sup>29\*</sup> Clive<sup>31\*</sup> and Reich<sup>32\*</sup> recently appeared which covering inter alia such field. However, we will briefly present the transformations performed on the molecules prepared from  $\alpha$ -selenocarbonions and electrophiles and which lead to selenium free compounds.

The removal of the selenyl moiety can be achieved either by the selective attack of the reagent directly on the selenium atom (Eq. 161, route a) or by the selective activation of another functional group present in the molecule and the participation, due to its proximity, of the selenyl moiety (Eq. 161, route b).



#### III C1 Reduction of the carbon-selenium bond

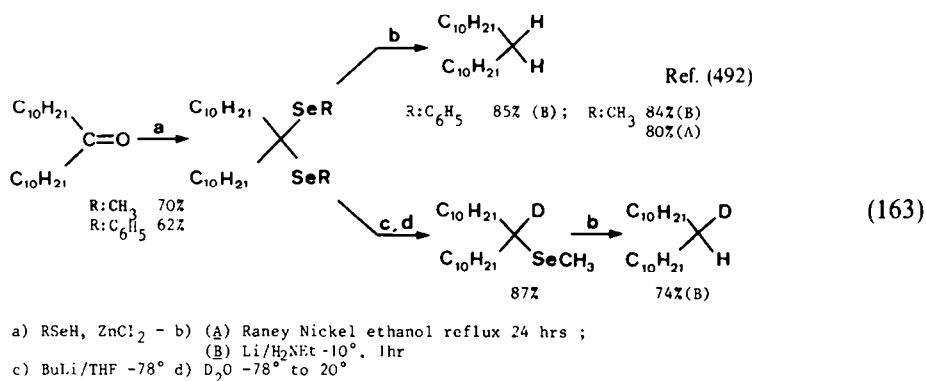
Selenides and selenoacetals can readily be reduced to the corresponding alkanes in good to high yield when reacted with Raney Nickel in ethanol at reflux for 20 hr (method A),<sup>492</sup> lithium in ethyl amine at  $-10^\circ$  for 2 hr (method B)<sup>492</sup> or with an excess of triphenyl or tributyl tin hydride (2–3 equiv.) in benzene at reflux for 1–2 hr (method C)<sup>498</sup> (Eqs. 162, 163, 164).



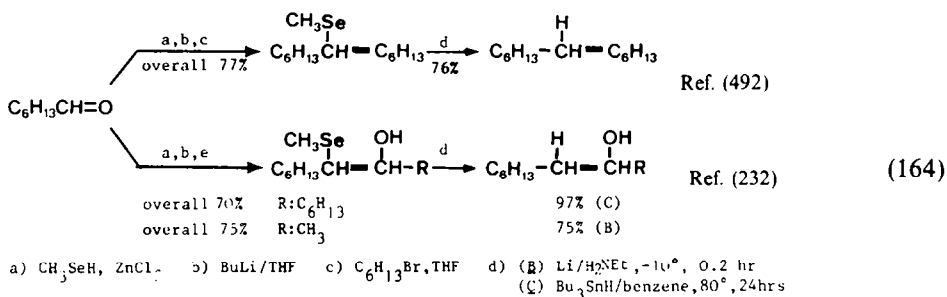
All the methods seem to be convenient for this transformation, however the choice of one specific method depends on the nature of the synthetic problem to be solved. Method B is particularly simple but it is not compatible with the presence of several other functional groups in the molecule.<sup>241\*</sup> Raney Nickel (method A) requires a long reaction time, but it is thought to be quite selective, method C seems to be the most selective but the by-products of the reaction are particularly difficult to remove especially when simple alkanes are formed.<sup>498</sup>

The Li–H<sub>2</sub>NEt or Bu<sub>3</sub>SnH methods selectively allow the high yield synthesis of alcohols from  $\beta$ -hydroxyselenides<sup>232</sup> whereas the corresponding acetates on reaction with lithium in ethyl amine (method B)<sup>499</sup> lead to a mixture of compounds<sup>232</sup> consisting in olefin (10% from  $\beta$  elimination reaction), alcohols (32%) and the corresponding alkanes (40%).

As selenoacetals and selenides are easily prepared from aldehydes and ketones, the whole processes described in Eqs. (163), (164) allow the reduction (Eq. 163), the reductive alkylation (Eq. 164) or the reductive (hydroxy) alkylation of aldehydes and ketones.



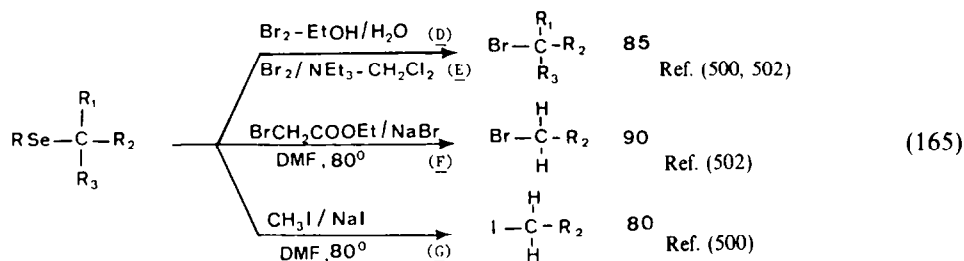
(163)



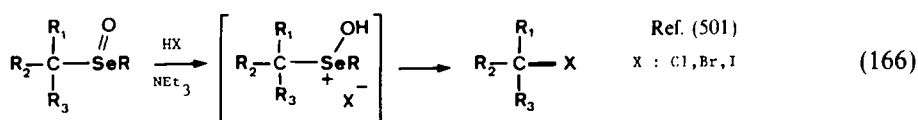
(164)

### III C2 Selenides are valuable precursors of alkylhalides

Alkylbromides are directly prepared from selenides and bromine in ethanol-water (80°, 3 hr, method D),<sup>500</sup> bromine in methylene chloride in the presence of triethylamine (20°, 3 hr, method E),<sup>500</sup> N-bromosuccinimide in ethanol-water (80°, 3 hr, method D')<sup>500</sup> or when selenides are refluxed in DMF with alkyl bromoacetates and sodium bromide (80°, 48 hr, method F).<sup>502</sup> Closely related to this last reaction is the synthesis of alkyl iodides from primary alkylselenides, methyl iodide and sodium iodide (DMF, 80°, 5 hr, method G)<sup>136, 500</sup> and which occurs in particularly high yield performed in the presence of CaCO<sub>3</sub> as a base (method G')<sup>502b</sup> (Eqs. 165, 167-171).



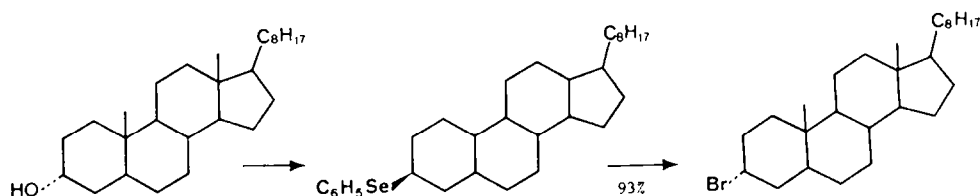
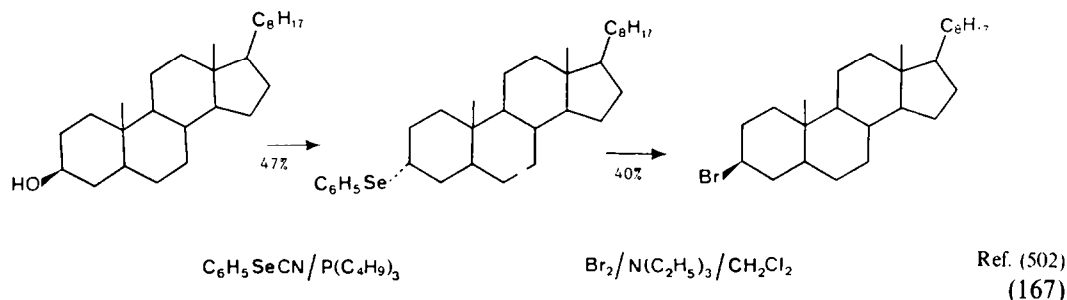
We also found that alkylchlorides, bromides and iodides can be obtained when selenoxides [easily prepared from selenides by ozone or from  $\alpha$ -lithioselenoxides and electrophiles<sup>116, 31\*, 32\*</sup>] are reacted with hydrochloric,<sup>501</sup> hydrobromic<sup>501</sup> or hydroiodic<sup>232</sup> acid in the presence of triethyl amine (20°, 2.5 hr, method H) (Eq. 166, 169).



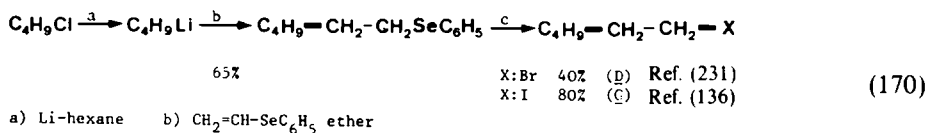
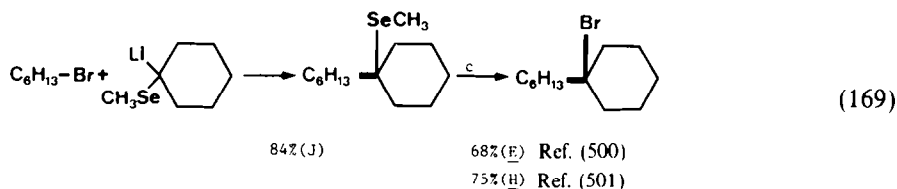
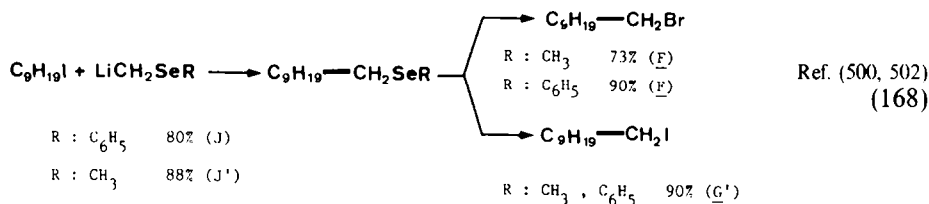
Methods *D*, *D'*, *E*, *H* work particularly well with secondary or tertiaryalkyl- methyl- or phenylselenides or selenoxides but are ineffective for primary alkyl ones.<sup>500,501</sup> At the contrary, methods *F*, *G*, *G'* are very efficient with primary alkyl selenides but require longer reaction time for higher homologues and produce large amount of olefins beside the desired alkylhalides.<sup>4b\*, 500, 501, 502b</sup>

All the reactions described (methods *D*–*H*) are highly regioselective. Reactions *D* and *E* were found to be stereospecific and occur with complete inversion of configuration.<sup>502</sup>

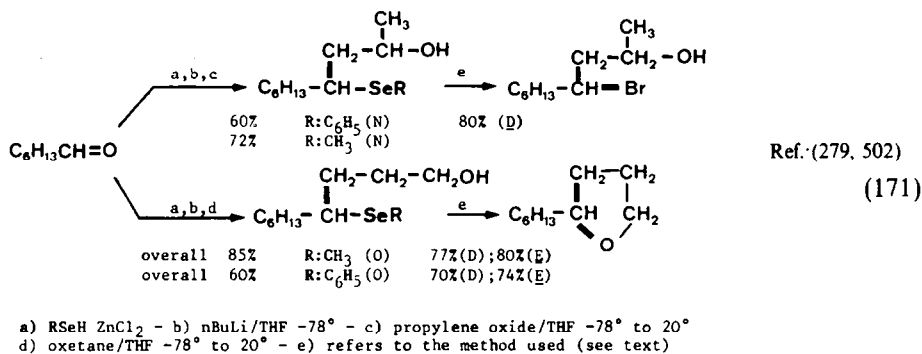
Connected to the Grieco reaction<sup>503</sup> which allows the stereospecific<sup>502</sup> synthesis of phenylselenides from alcohols with inversion of configuration, our reactions (*D*, *E*) permits the two steps synthesis of alkyl bromides from alcohols with total overall retention of configuration. This is exemplified on two isomeric cholestanols (eqn. 167).



The reactions presented in Eqs. (168), (169), describe new ||||| homologization reactions of primary alkylhalides which occur *via a process similar to carbene insertion between the alkyl group and the halogen atom*.<sup>500–502</sup> Whereas the transformations shown in Eq. (170)<sup>136, 231</sup> allow alkylhalide synthesis by formal addition of an alkyl halide to ethylene.



Some of the reactions described (methods *D* and *G*) have been successfully applied to  $\beta$ - and  $\gamma$ -hydroxyselenides producing respectively  $\beta$ -bromo<sup>500</sup> and  $\gamma$ -bromo alcohols<sup>279,502b</sup> (Eq. 171), the last reaction is completely stereospecific producing specifically one  $\gamma$ -bromo alcohol when only one stereoisomer of  $\gamma$ -hydroxyselenide is used.<sup>279,502b</sup> Interestingly,  $\delta$ -hydroxyselenides are directly cyclised to furanes under similar conditions<sup>279</sup> (methods *D-F*) (Eq. 171).



The reactions described in the above equation (Eq. 171) permit the selective halogeno ( $\gamma$ -hydroxy) alkylation of carbonyl compounds or their selective transformation to furanes by formal insertion of the 1-3 dipole CH<sub>2</sub>-CH<sub>2</sub>-CH in between the carbon oxygen bond of the carbonyl group.

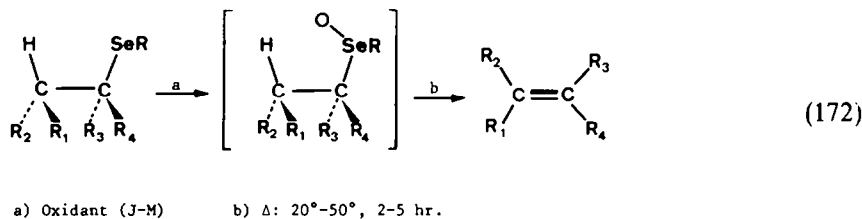
### IIC3 Olefins syntheseses from selenides

#### (a) Olefin formation via the selenoxide route.

Selenides have been transformed to olefins via selenoxide formation followed by selenenic acid *syn* elimination<sup>505</sup> or via the selenonium salt formation followed by  $\beta$ -elimination reaction.<sup>509</sup>

The selenoxide route was introduced at the synthetic level by Sharpless,<sup>29\*, 504\*, 505</sup> Clive<sup>31\*</sup> and Reich<sup>32\*</sup> who vastly reviewed the subject. Thus we will not do it again but will only present specific problems in this field and their solutions. The interest of this reaction arises from the mildness of the conditions reaction needed for the olefin synthesis, compared to those required for related sulfoxide and aminoxide elimination (relative temperature range for  $\alpha,\beta$ -disubstituted olefin synthesis 20°:140°:240°.<sup>32\*</sup>

As already mentioned the reaction occurs in two distinct steps (Eq. 172). The first one, namely the oxidative reaction of selenides to selenoxides is very easy (much more than in sulfides) and interestingly the over oxidation to selenone is a difficult reaction<sup>32\*</sup> (this is not the case with sulfur analogues). Thus selenoxides are quite quantitatively formed under a large variety of experimental conditions including: hydrogen peroxide in THF (method *I*), ozone in chlorinated hydrocarbons (method *J*), organic peracids (method *K*), t-Butyl hydroperoxide (method *L*) or singlet oxygen.<sup>507</sup>



The selenenic acid elimination is the rate determining step and the ease of olefin formation depends on the nature of the substituents attached to the selenium atom. It is usually rapid when electron withdrawing groups are linked to the selenium atom and becomes difficult in case of alkyl groups [R: p-nitro phenyl > m-chlorophenyl > phenyl >> methyl (Eq. 172)].<sup>29\*, 31\*, 32\*, 503, 525, 526</sup>

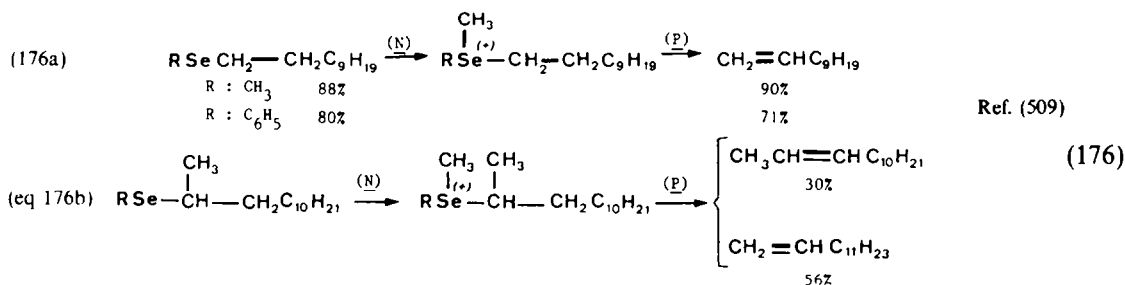
Selenoxide elimination is easier when the selenyl moiety is branched  $\alpha$  to carbonyl groups, or at a benzylic position and gradually decreases from secondary alkyl selenides to primary ones which are the most difficult to eliminate. The worst being primary alkyl methylselenides.<sup>506</sup> For examples



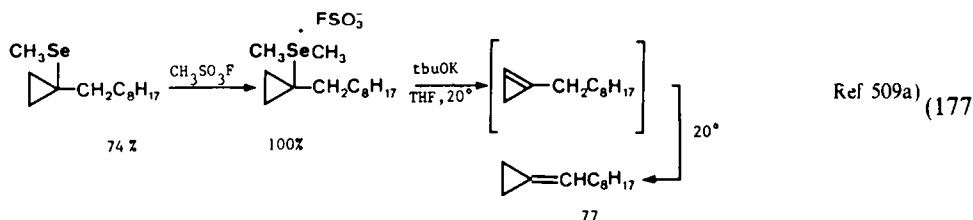


ammonium<sup>9\*,261a</sup> and selenonium<sup>9\*,261b</sup> salts. It takes advantage of the methylation of selenides [ $\text{CH}_3\text{I}$ ,  $\text{AgBF}_4$ ,  $20^\circ$  (method *N*) or  $\text{CH}_3\text{SO}_3\text{F}$ , ether,  $20^\circ$ , (method *O*)] and the formation of olefins<sup>509</sup> when the resulting selenonium salts are reacted at  $20^\circ$  with bases such as *t*-BuOK in THF (method *P*), *t*-BuOK in DMSO (method *Q*), KOH in THF (method *R*), KOH in DMSO (method *S*).

Under these conditions, terminal olefins are regiospecifically formed from primary alkylselenides, (Eq. 176a) whereas a mixture of olefins in which the terminal ones predominates is obtained from sec.alkylselenides (2–5 hr, 80–90% yield).

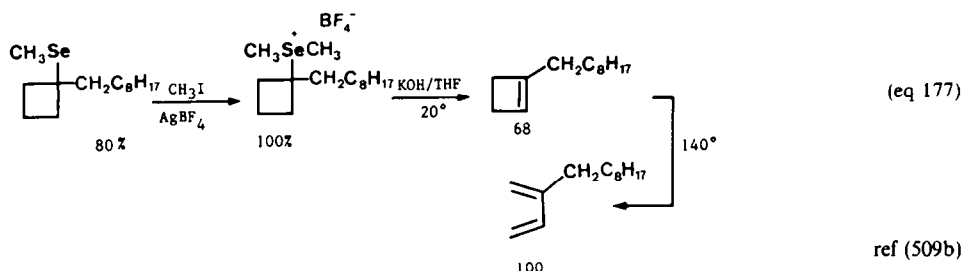


Methods *P* and *Q* are particularly suitable for the synthesis of alkylidene cyclopropanes<sup>509</sup> from the corresponding cyclopropyl selenonium salts, themselves easily prepared from cyclopropyl selenides (Eq. 177). The elimination reaction is slower than in open chain derivatives due to the strain introduced during the transformation and requires 40 hr at  $20^\circ$  to go to completion. Cyclopropene is kinetically formed but the rate of isomerisation to the more stable alkylidene cyclopropane is faster than the elimination reaction.<sup>509a</sup>



This last reaction is particularly valuable since the selenoxide route is tedious when applied to cyclopropyl selenides<sup>509a</sup> requiring high temperature ( $120^\circ$ ), long period of heating (20 hr and producing low yield of alkylidene cyclopropanes ( $\sim 20\text{--}30\%$ )).

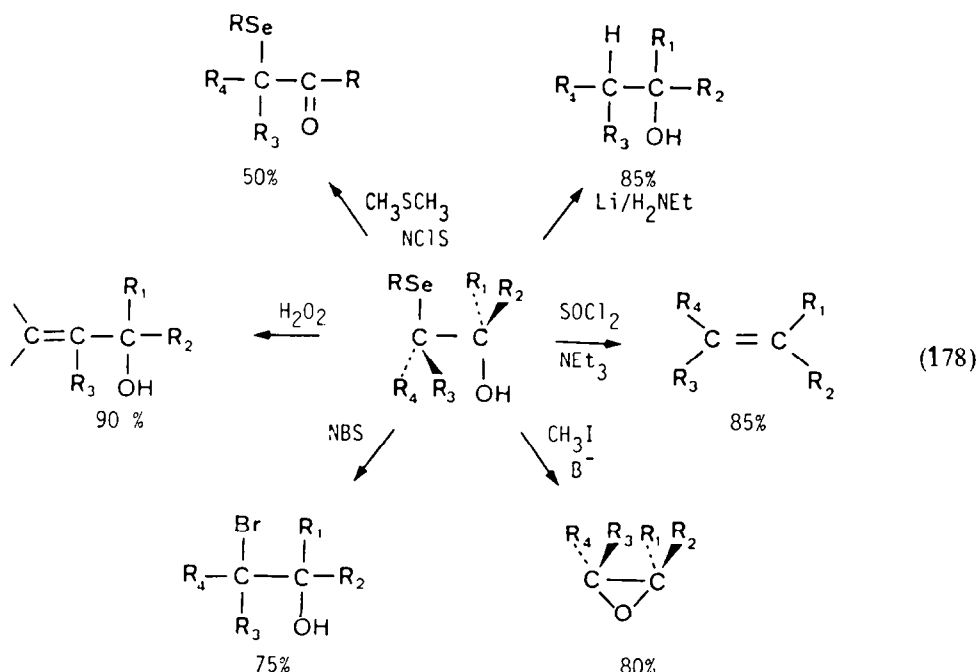
The selenonium salt route is also valuable in the cyclobutyl series<sup>509b</sup> since the cyclobutene, precursor of diene, is regioselectively (90%) formed (Eq. 177b) whereas a 1:1 mixture of the cyclobutene and alkylidene cyclobutene is obtained (in 68% yield) via the selenoxide route.<sup>509b</sup>



#### III C4 $\beta$ -hydroxyselenides transformations

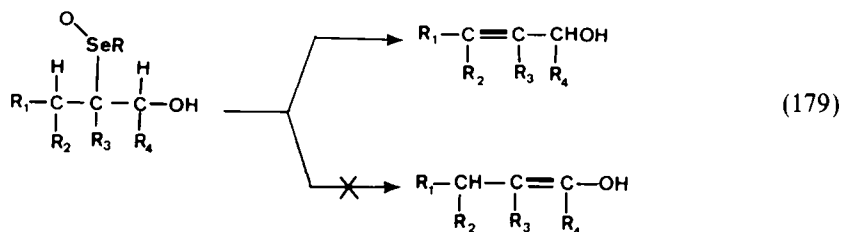
$\beta$ -Hydroxyselenides are one of the most valuable selenium containing molecules. They are easily prepared by ring opening of epoxides by selenolates:++++<sup>29\*,58,60</sup> by addition of hypothetical selenenic acid on olefins,++++<sup>510-512</sup> by deacetylation of  $\beta$ -acetoxy selenides,++++<sup>31\*,513-515</sup> by substitution reaction on  $\beta$ -halogeno selenides++++<sup>516</sup> and with concomitant new C–C bond formation from  $\alpha$ -selenoalkyllithiums and carbonyl compounds,<sup>58,60,61,75-77,186,220,221,229,232,495,496,509</sup> from  $\alpha$ -lithio selenoxides and carbonyl compounds followed by reduction of the resulting  $\beta$ -hydroxyselenoxides<sup>57</sup> and by reaction of organometallics on  $\alpha$ -selenocarbonyl

++++ These reactions occur stereoselectively.



compounds.<sup>59</sup> They have been selectively transformed to a large variety of derivatives free of selenium such as allyl alcohols,  $\alpha,\beta$ -unsaturated carbonyl compounds, olefins, epoxides, rearranged ketones and  $\alpha$ -selenocarbonyl compounds. These transformations are the subject of this paragraph.

(a) *Synthesis of allylic alcohols from  $\beta$ -hydroxyselenides.* This valuable transformation occurs in the presence of oxidants.<sup>29\*,31\*,32\*,220,221,229,495,496,504,509b</sup>  $\beta$ -Hydroxyselenoxides are easily formed (Chapter IIIC3a) and the selenenic acid specifically eliminates away from the hydroxyl function (Eq. 179).



Hydrogen peroxide in THF (method *I*)<sup>29\*,31\*,32\*</sup> is the choice reagent for the phenylseleno derivatives which are transformed at 20° and in few hours (2–4) into the corresponding allylic alcohols (Table X). Under these conditions however  $\beta$ -hydroxy phenylselenoalkanes, bearing a phenylseleno moiety attached to a cyclohexyl ring<sup>221</sup> or to a primary OH group<sup>495</sup> as well as all  $\beta$ -hydroxymethylselenides<sup>495</sup> produce very low yields of allyl alcohols. In the last two cases, *t*-butylhydroperoxide/alumina method (method *M*)<sup>495,506</sup> proved to be particularly useful (Table X).

Allyl alcohols possessing a disubstituted double bond consist quite exclusively on the *trans* isomers<sup>229,504</sup> when the OH function is attached to a disubstituted C atom whereas a 72/25 *E/Z* mixture of the two stereoisomers is observed in case of a primary hydrogen group.<sup>495</sup>

Connective routes to allyl alcohols, with new C–C bond functions which include the use of  $\alpha$ -selenoxy alkylolithiums and  $\alpha$ -selenoalkylolithiums are presented in eqns (180–181) and in Table X.

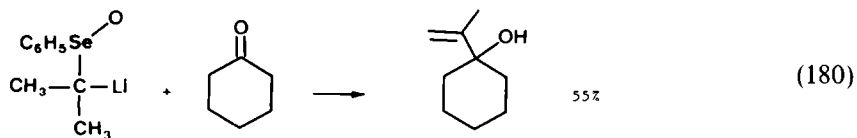
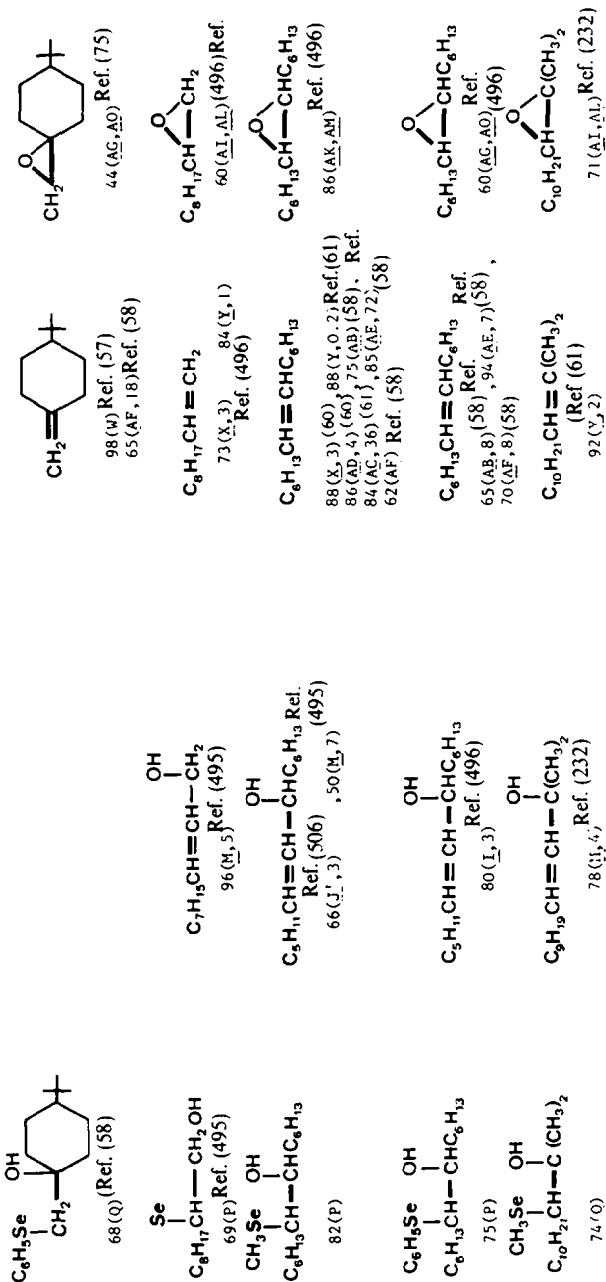
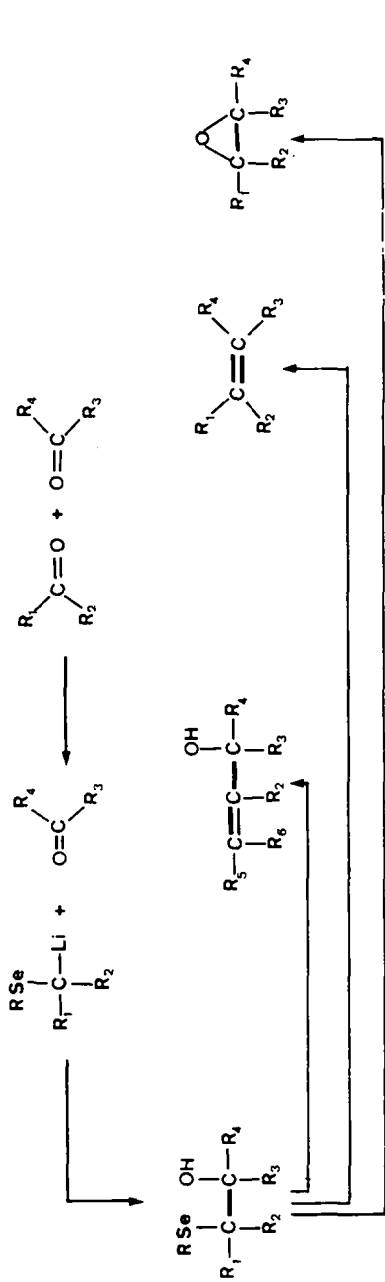
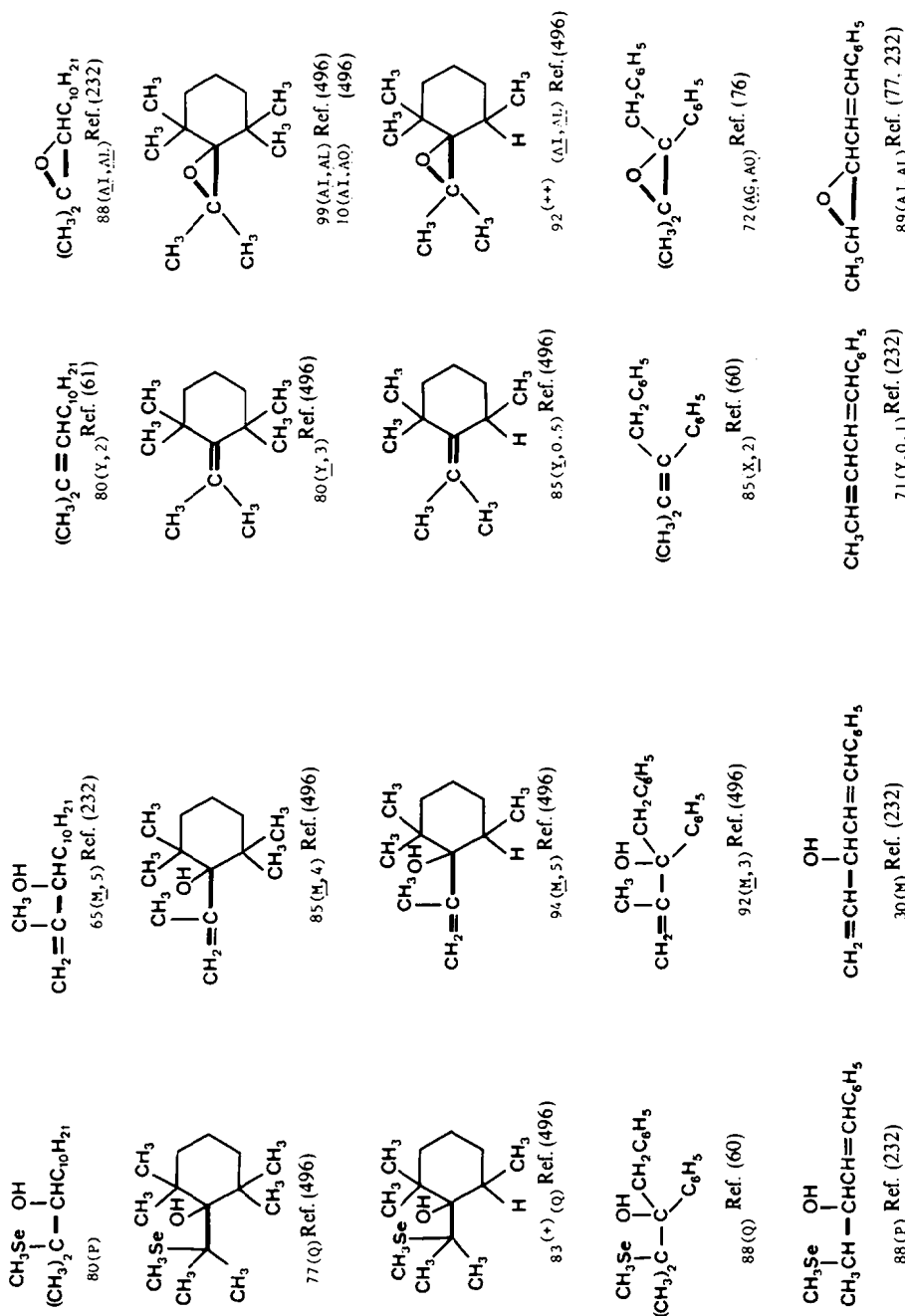


Table X.

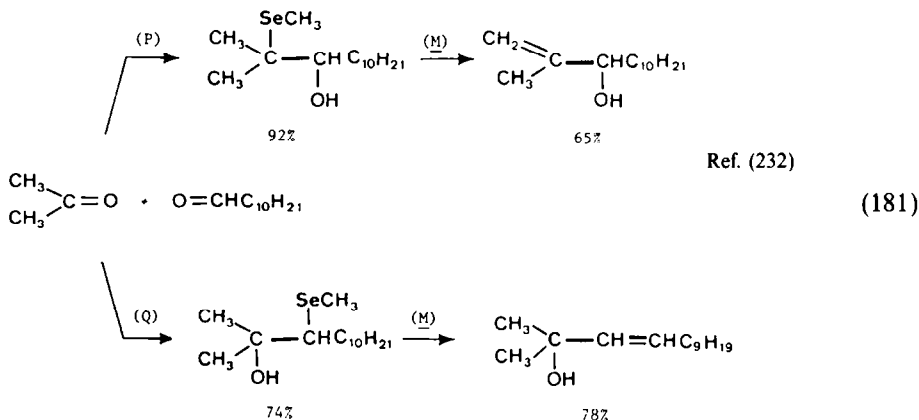




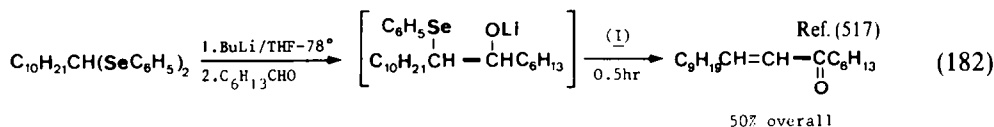
(\*) in ether; (\*\*) unstable

(I)  $\text{H}_2\text{O}_2/\text{THF}$ , 20°; (J')  $\text{O}_3$ ;  $\text{NET}_3/\text{CH}_2\text{Cl}_2$ , 45°; (M)  $\text{tBuO}_2\text{H}/\text{Al}_2\text{O}_3/\text{THF}$ , 55°; (N)  $\text{MeSCl}/\text{CH}_2\text{Cl}_2$ ,  $\text{NET}_3$ , 20°; (X)  $\text{SOCl}_2/\text{NET}_3/\text{CH}_2\text{Cl}_2$ , 20°; (Y)  $\text{PI}_3/\text{NET}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; (AB)  $(\text{CF}_3\text{CO})_2\text{O}$ ,  $\text{NET}_3$ ,  $\text{CH}_2\text{Cl}_2$ ; (AC) carbonyl diimidazole, 110°; (AE)  $\text{HClO}_4$ , ether, 20°; (AF)  $p\text{TosOH}$ , benzene reflux; (AG)  $\text{CH}_3\text{I}/\text{AgBF}_4$ ; (AI) Magic Methyl/Ether; (AJ)  $\text{CH}_3\text{I}$  neat; (AK)  $(\text{CH}_3)_2\text{SO}_4$  neat; (AL) aq  $\text{KOH}$  (10%) in ether; (AM) aq  $\text{KOH}$  (10%) in  $\text{CH}_2\text{Cl}_2$ ; (AO)  $\text{tBuOK}$  in DMSO.

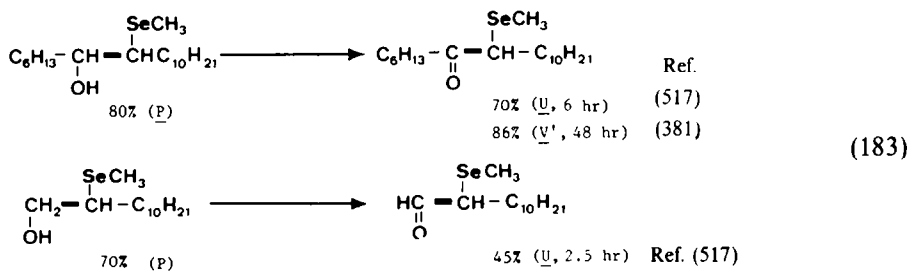
Interestingly, the whole transformation presented in Eq. (181) allows regioselective synthesis of each of the two regioisomers of allyl alcohols from two carbonyl compounds each one being selectively activated as a selenoacetal.<sup>220, 221, 229, 232, 495, 509b</sup>



(b)  $\alpha,\beta$ -Unsaturated carbonyl compounds synthesis can be classically achieved by  $\text{MnO}_2$  oxidation of the allyl alcohols prepared above. Another convenient reaction<sup>517</sup> performed in one pot, takes advantage of the in situ oxidation of  $\beta$ -selenoalcoholates, prepared from  $\alpha$ -selenoalkyllithiums and carbonyl compounds, with Jones reagent ( $\text{CrO}_3/\text{H}_2\text{SO}_4/\text{THF}$ ;  $60^\circ$ ; 0.5 hr, method *T*) (Eq. 182).



(c)  $\alpha$ -Seleno carbonyl compounds $\ddagger\ddagger\ddagger\ddagger$  synthesis from  $\beta$ -hydroxyselenides is quite a challenge since the OH group must be selectively oxidized in the presence of a selenyl moiety, known to be very easily oxidized by a variety of oxidants (see e.g. para. IIIC3a and IIIC4a, b). The Corey–Kim reagent<sup>518</sup> ( $(\text{CH}_3)_2\text{S}-\text{NCIS}-\text{NEt}_3$ , in toluene or methylene chloride, method *U*) (Eq. 183)<sup>517, 519</sup> and the Posner reaction using chloral on activated alumina<sup>520</sup> (method *V*) were found amongst a huge variety of tested<sup>517</sup> oxidants, the only ones suitable for such transformation. Recently, Barton successfully used<sup>381</sup> triphenyl bismuth carbonate for this purpose [ $(\text{C}_6\text{H}_5)_3\text{BiCO}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $50^\circ$ , 48 hr, method *V'*].

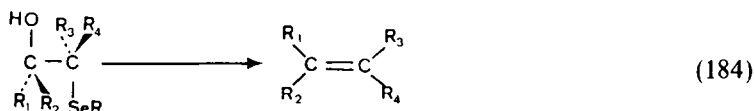


(d)  $\beta$ -Hydroxyselenides are selectively reduced, as already mentioned (Chapter IIIC1) to alcohols<sup>232</sup> by lithium in ethyl amine or tributyl tin hydride (Eq. 164) and interestingly no significant amount of olefin, which could arise from  $\beta$ -elimination reaction was observed.<sup>232</sup> This reaction was further used by Nicolaou for the deselenylation of  $\beta$ -selenoester and  $\alpha$ -selenolactones.<sup>530</sup>

(e)  $\beta$ -Hydroxyselenides are valuable precursors of olefins. This transformation (Eq. 184) is observed every time the OH group is transformed to a powerful leaving group and is related to the strong

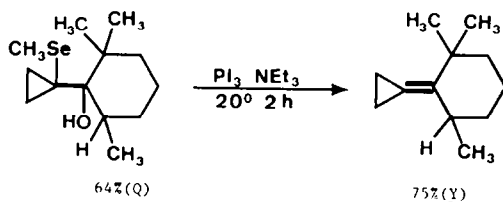
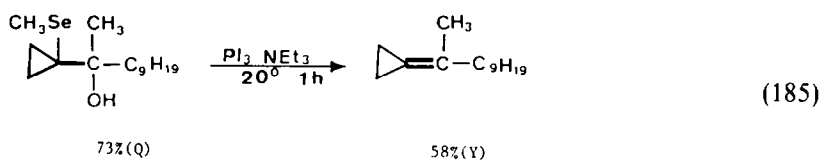
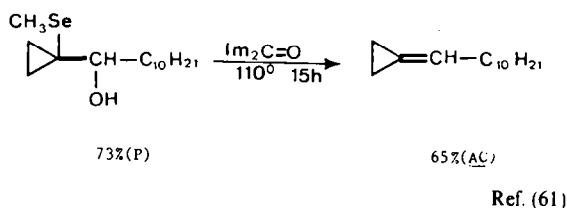
$\ddagger\ddagger\ddagger\ddagger$  For other synthesis of  $\alpha$ -seleno carbonyl compounds, see Refs. 29\*, 31\*, 32\*, 245, 497, 521, 522, 529, 535.

neighbouring group participation of the Se atom. It occurs in neutral, basic or acid media with a large variety of reagents such as mesylchloride (method *W*),<sup>57</sup> thionylchloride (method *X*),<sup>59,60,496</sup> phosphorus triiodide (method *Y*) or diphosphorus tetraiodide (method *Z*),<sup>61</sup> phosphorus oxychloride (method *AA*)<sup>246</sup> or trifluoroacetic anhydride (method *AB*).<sup>§§§§§</sup><sup>58</sup> These reactions are performed in methylene chloride usually in the presence of triethylamine (which seems required for the success of the transformation: (Chapter III C4f) at 20° for 3–10 hr. Other experimental conditions include their reaction with carbonyl diimidazole in toluene at 100° (method *AC*),<sup>§§§§§</sup><sup>61</sup> phosphochloridate in presence of sodium hydride (method *AD*)<sup>60</sup> as well as with perchloric acid in ether at 20° (method *AE*)<sup>58</sup> or *p*-toluenesulfonic acid in pentane at reflux (method *AF*).<sup>58</sup>



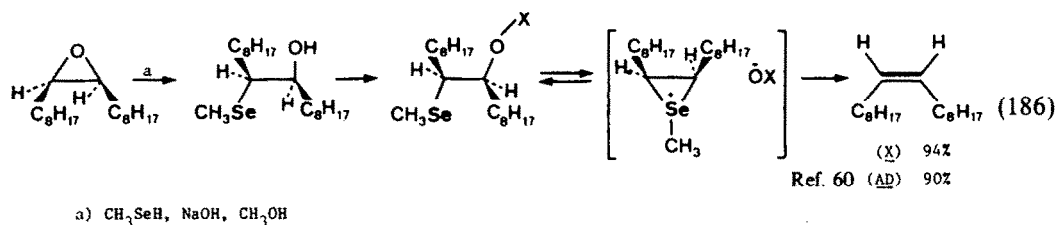
Methods *W*, *X*, *Y*, *Z*, *AA* allow the high yield synthesis of terminal di-, tri- and tetra-substituted olefins, and  $\alpha,\beta$ -unsaturated esters and lactones<sup>246</sup> from the corresponding  $\beta$ -hydroxy(phenyl or methyl)selenides (Table X). Acidic conditions (methods *AE*, *AF*) work fine with  $\alpha,\beta$ -disubstituted  $\beta$ -hydroxyselenides but lead to a mixture of olefins and rearranged ketones<sup>58</sup> in case of tri- or tetra-substituted  $\beta$ -hydroxyselenides.

$\beta$ -Hydroxycyclopropyl selenides are particularly difficult to transform to alkylidene cyclopropanes due to the strain introduced during this reaction. We however succeeded<sup>61</sup> this transformation by heating the  $\beta$ -hydroxyselenides derived from aldehydes with carbonyldiimidazole (method *AC*) or by reacting those derived from ketones with  $\text{PI}_3$  at 20° (method *Y*) (Eq. 185).



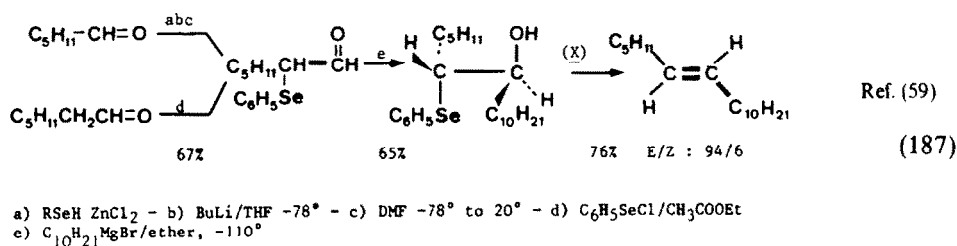
In the cases studied: i.e. di- and tri-substituted  $\beta$ -hydroxyselenides and thionylchloride (method *X*) or phosphochloridate (method *AE*), the transformation was found highly stereospecific<sup>58-60</sup> and occurs by formal anti elimination of both hydroxyl and selenyl moieties (Eq. 186, 187).

§§§§§ These methods should be valuable in sugar chemistry since the other OH groups present can be intact by hydrolysis after olefin formation.



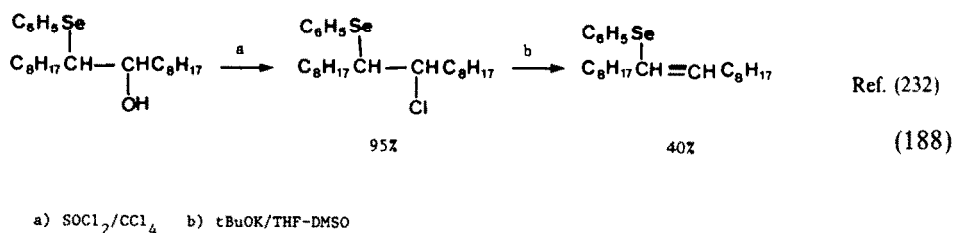
We suspected the intermediacy of a seleniiranium salt and proved that a preformed seleniiranium salt is quantitatively and stereospecifically transformed to the corresponding olefin in the presence of triethylamine.<sup>60</sup>

The transformation presented in this paragraph is valuable in synthesis. Coupled with the stereospecific ring opening of epoxide by selenolate, it allows the stereospecific *cis* deoxygenation of di- and tri-substituted epoxides<sup>58, 60</sup> (Eq. 186). And, since  $\beta$ -hydroxyselenides are available in high yield from  $\alpha$ -selenoalkyllithiums and carbonyl compounds, even those highly uncumbered or enolisable (Table X) this two pots reaction can be successfully compared<sup>57, 58, 60, 61</sup> to the Wittig reaction which does not work for the two later cited cases. Finally, it allows the stereospecific olefin synthesis with new C-C bonds formation when coupled with the reaction of organometallics and  $\alpha$ -selenocarbonyl compounds<sup>59</sup> (Eq. 187).

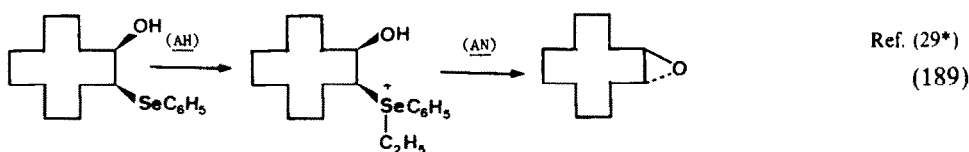


(f) *Synthesis of  $\beta$ -chloroselenides and vinylselenides.* Recent results show the presence of triethylamine, essential for the success of olefin synthesis from  $\beta$ -hydroxyselenides and thionyl chloride. For example, 9-hydroxy-10-phenylseleno octadecane which exclusively leads to 9-octadecene on reaction with thionyl chloride triethylamine in methylene chloride (90% yield), exclusively produce 9-chloro-10-phenylseleno octadecane when triethylamine is omitted.

This  $\beta$ -chloroselenide was transformed to a mixture of 9-phenylseleno-9-octadecene (40%) and 9-octadecene (~40%) on treatment with *t*-BuOK in THF-DMSO (Eq. 188).



(g)  *$\beta$ -Hydroxyselenides lead to epoxides* when alkylated at selenium and when the resulting  $\beta$ -hydroxyselenonium salt is further reacted with base<sup>29, 31, 59, 75, 76, 232, 496</sup> (Eq. 189).



Olefins formed that way consist in a mixture of the two stereoisomers since the two stereoisomers of  $\beta$ -hydroxyselenides are obtained from  $\alpha$ -selenoalkyllithiums and carbonyl compounds (Chapter IIIB).

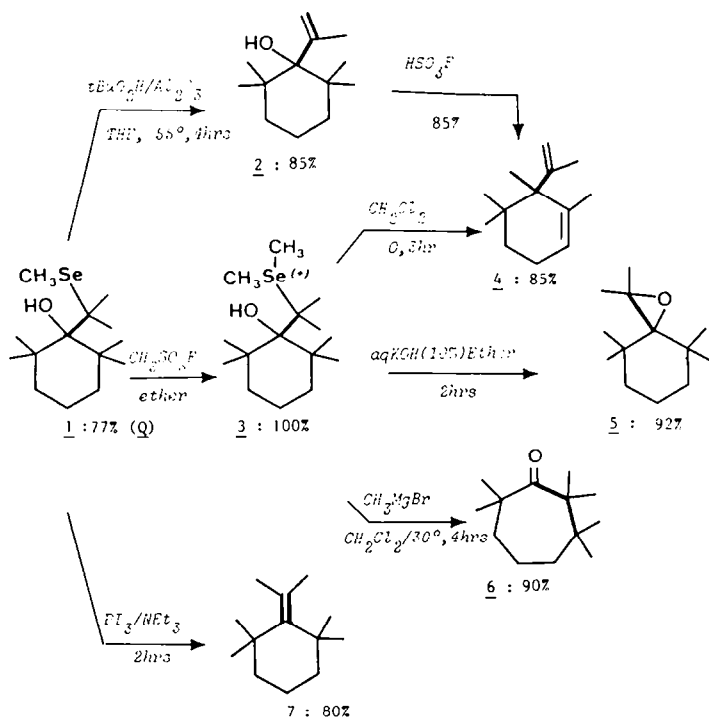


( $\alpha$ ) The first step of the reaction, namely the synthesis of the  $\beta$ -hydroxyselenonium salt is usually easy to perform. Phenylseleno derivatives require strong alkylating agents such as  $\text{CH}_3\text{I}/\text{AgBF}_4$  (method *AG*),<sup>75</sup> triethyloxonium fluoroborate (method *AH*)<sup>29\*</sup> or magic methyl (method *AI*).<sup>496</sup> Under these conditions,  $\beta$ -hydroxyselenonium salts are quantitatively prepared when the selenyl moiety is attached to a primary or a secondary carbon atom (Table X), whereas ketones resulting from a rearrangement are often formed in the case of tertiary selenides.<sup>75</sup> This last transformation is similar to a carbene insertion  $\alpha$  to the carbonyl group.

$\beta$ -Hydroxymethylselenides react much easily, even substantially more easily, than alkylmethylselenides<sup>509</sup> (cf to Chapter IIIC3b) probably due to the assistance of the  $\beta$ -OH group. Methyl iodide (method *AJ*)<sup>76,77</sup> or methyl sulfate (method *AK*) (in ether but better neat)<sup>76,77</sup> are strong enough to allow the quantitative alkylation of the selenium atom (20°, 2–12 hr) even with tetrasubstituted  $\beta$ -hydroxyselenides (Table X). However magic methyl (method *AI*)<sup>496</sup> is particularly useful, since the reaction can be performed in ether at low temperature (–40° to 20°, 2 hr) if short reaction times are needed, if the starting material is especially hindered or when the resulting selenium salts are thermally sensitives<sup>496</sup> (3, Eq. 190).

( $\beta$ )  $\beta$ -Hydroxyselenonium salts are stereoselectively transformed to epoxides on reaction with bases. Aqueous KOH (10%) in ether (method *AL*)<sup>496</sup> or in  $\text{CH}_2\text{Cl}_2$  (method *AM*),<sup>496</sup> NaH in THF (method *AN*)<sup>29\*</sup> and *t*-BuOK in DMSO (method *AO*)<sup>59,75–77</sup> proved to be satisfactory (Table X).

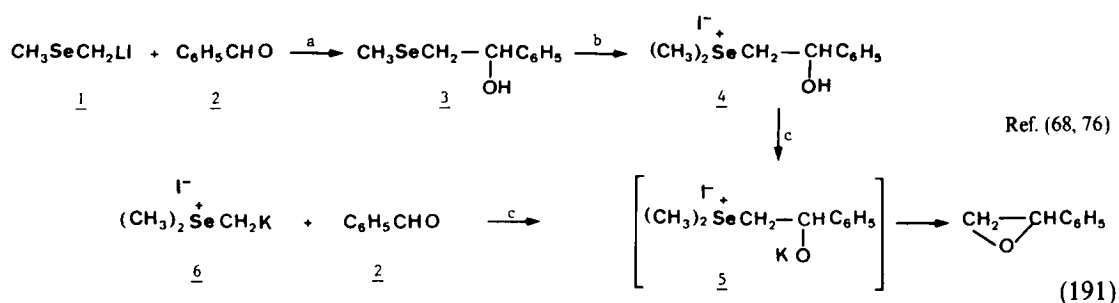
In some special cases such as the selenonium salt derived from reaction of 2-lithio 2-selenopropane and 2,2,6,6-tetramethylcyclohexanone<sup>496</sup> (Eq. 188), method *AO* mainly produces the allyl alcohol whereas the epoxide is quantitatively formed using method *AL*<sup>496</sup> (Eq. 190). Method *AM* is not suitable in that case since the salt rapidly rearranges in  $\text{CH}_2\text{Cl}_2$  and produces<sup>496</sup> a mixture of 4, 5 and 6 (Eq. 190).



Ref. (496)  
(190)

The reaction performed on methyl seleno derivatives are particularly valuable since terminal-, di-, tri- and tetra-substituted epoxides are obtained quite quantitatively and free from any by-product. This is due to the great volatility of the dimethyl selenide obtained at the last stage of the synthesis.<sup>76</sup> In all the cases a betaine (5, Eq. 191) is postulated as an intermediate. This betaine was already postulated on reaction of carbonyl compounds with selenium ylides<sup>68</sup> (6, Eq. 191).

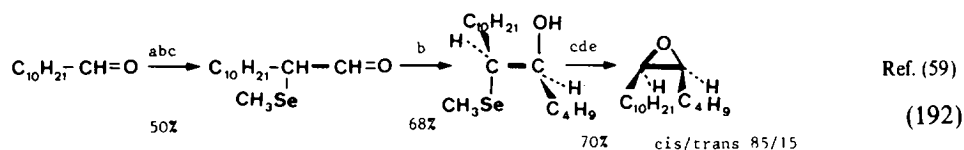
Epoxides synthesis has been achieved with concomitant new C–C bond formation from  $\alpha$ -seleno carbonyl compounds and hydrides or grignard reagents (Eq. 192)<sup>59</sup> or from  $\alpha$ -seleno alkylolithiums and carbonyl compounds (Eq. 190, Table X).<sup>76,77,496</sup>



a) THF -78° - b) CH<sub>3</sub>I neat - c) tBuOK-DMSO

The first method allows the stereoselective synthesis of disubstituted epoxides<sup>59</sup> (Eq. 192).

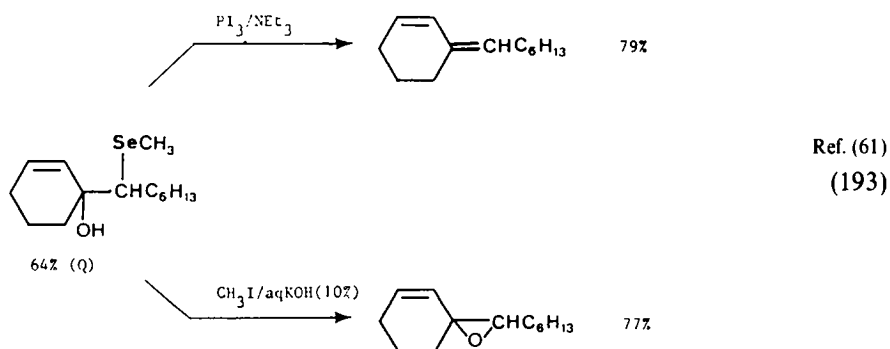
The second one is particularly interesting since it provides a smooth entry to epoxides||||||| even for those derived from highly uncumbered carbonyl compounds such as 2,2,6,6-tetramethyl cyclohexanone (Eq. (190), Table X) or highly enolisable ones such as deoxybenzoine or 2,2,6-trimethyl cyclohexanone (Table X) unavailable by the well known sulfur ylide reaction<sup>9\*,23\*,28\*</sup> which usually produce epoxides with similar bonds formation.



a) CH<sub>3</sub>SeH, ZnCl<sub>2</sub> - b) nBuLi THF -78° - c) DMF -78° to 20° then H<sub>3</sub>O<sup>+</sup>  
 d) C<sub>10</sub>H<sub>21</sub>MgBr, ether -78° - e) CH<sub>3</sub>I neat - f) tBuOK-DMSO

The methods disclosed (Chapters IIIC4e, IIIC4g) allow the high yield syntheses of olefins and from two carbonyl compounds, each of them being activated as a selenoalkyllithium depending the nature of the problem to be solved (Table X).

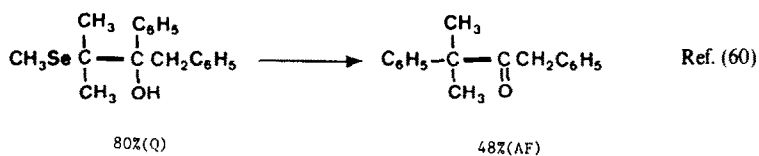
They have been successfully applied to the synthesis of dienes<sup>60, 232</sup> and α,β-unsaturated epoxides<sup>77, 232</sup> (Eq. 193).



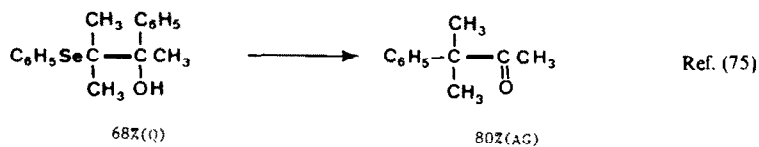
The products disclosed in Eq. (193) cannot be obtained from phosphorus and sulfur ylides and cyclohexenone (the same carbonyl compound) since enolisation of cyclohexenone is an important side reaction in the first case and because 1-4 addition reaction producing γ-oxophosphonium salt in the first case<sup>232</sup> and a cyclopropane in the second one<sup>232</sup> (see also Refs. 65, 28\*) compete.

(h) Carbonyl compounds have been in several instances noticed. When β-hydroxyselenides bearing the selenyl moiety on a trisubstituted carbon are reacted with alkylating agents or with acids (Chapters IIIC4e and IIIC4f) (Eq. 194).

||||||| The whole transformation is not stereoselective since the first step does not occur stereoselectively.



(194)

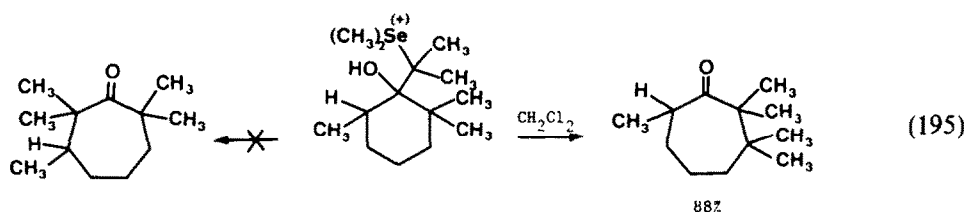


Ref. (75)

We have also shown<sup>496</sup> (Eq. 190) that the selenium salt **3** readily produces the diene **4** on heating at 60° or by simple dissolution in  $\text{CH}_2\text{Cl}_2$  at 20°. This diene probably arise by initial decomposition of the hydroxyselenonium salt to the corresponding carbonium ion and dimethylselenide (or to the allyl alcohol **2**, dimethylselenide and fluorosulfonic acid) and further migration of the Me group. This last transformation has been independently performed<sup>496</sup> by reacting fluorosulfonic acid with the allyl alcohol **2**.

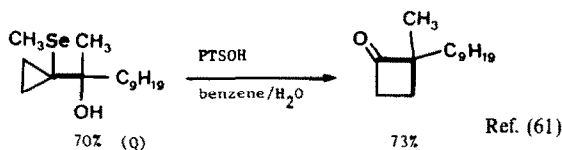
The Me migration can be avoided if the decomposition of the salt **3** is achieved under neutral condition in  $\text{CH}_2\text{Cl}_2$ .<sup>496</sup> Thus when Grignard reagent+++++ is used, the ring enlargement occurs leading to the rearranged ketone **6** quite quantitatively.<sup>496</sup>

The generality of such reaction is not yet established but the selenium salt derived from the less uncumbered 2,2,6-trimethylcyclohexanone (Eq. 195) behave similarly<sup>496</sup> allowing the synthesis of the 7-membered ring ketone by exclusive migration of the more substituted C atom.

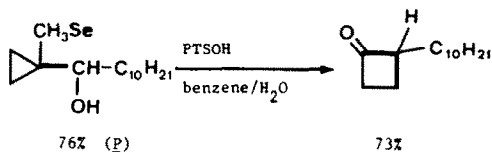


(195)

Finally, acid catalysed reaction of  $\beta$ -hydroxyselenides derived from 1-lithio-1-seleno cyclopropane produces cyclobutanones in high yield<sup>61</sup> (Eq. 196). This transformation is closely related to the one already described by Trost for sulfur analogues.<sup>523</sup>



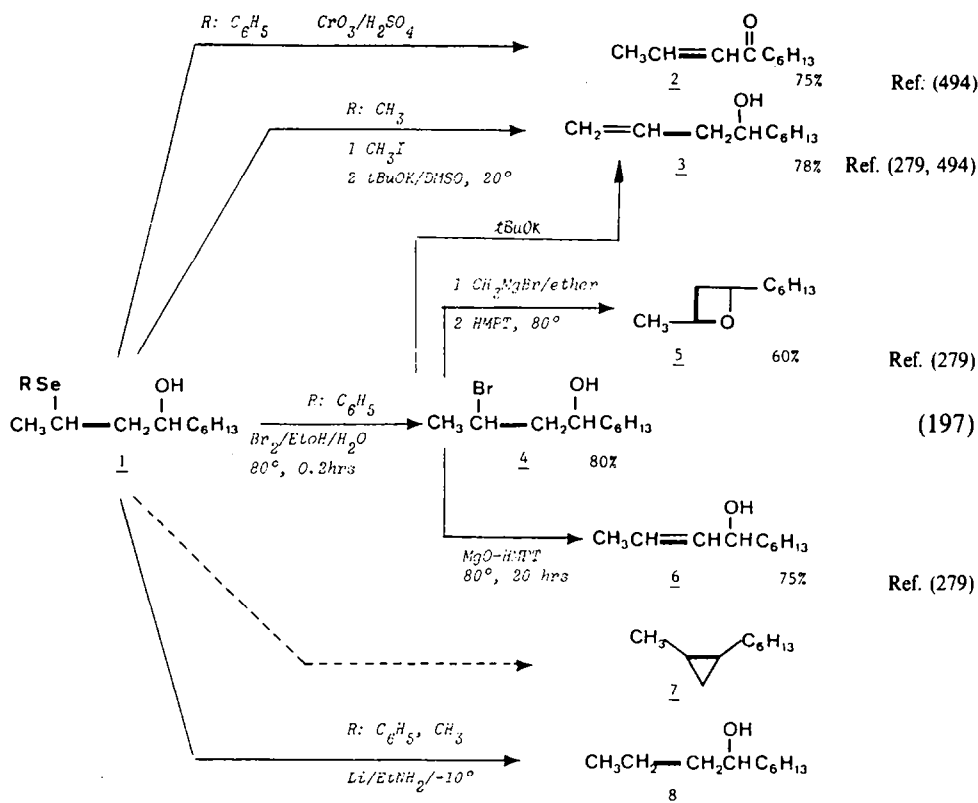
(196)



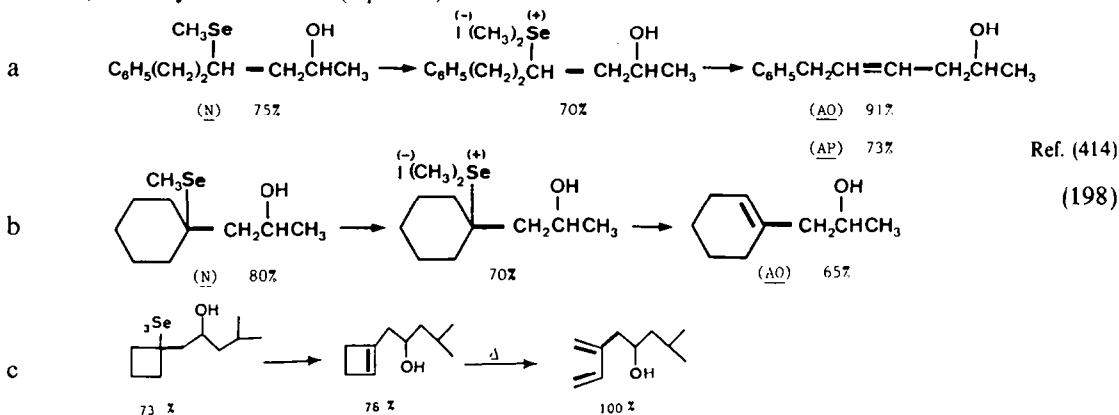
### IIIC5 Transformations using $\gamma$ -hydroxyselenides

$\gamma$ -Hydroxyselenides available from  $\alpha$ -selenoalkyllithiums and terminal epoxides have been selectively transformed to homoallyl alcohols,<sup>279,494</sup> allyl alcohols<sup>279</sup>  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>494</sup> and to oxetanes<sup>279</sup> (Eq. 197).

+++++ Which is unsuitable for the formation of epoxides (such as **5**, Eq. 190).



(a) The synthesis of homoallyl alcohols<sup>279,494</sup> takes advantage of the easy alkylation of the selenium atom in  $\gamma$ -hydroxymethylselenides by methyl iodide (neat, 20°, 5 hr) and the regioselective elimination of the selenide, promoted by *t*-BuOK in DMSO (20°, 4 hr) (method AO) or by aqueous KOH under phase transfer conditions (adogen 464, CH<sub>2</sub>Cl<sub>2</sub>, 20°) (method AP) (Eq. 198). The reaction has been recently used for the regioselective 100% synthesis of ipsenol,<sup>509b</sup> an aggregation pheromone of *Ips* *Barkae*, from cyclobutanone (eq 198c).

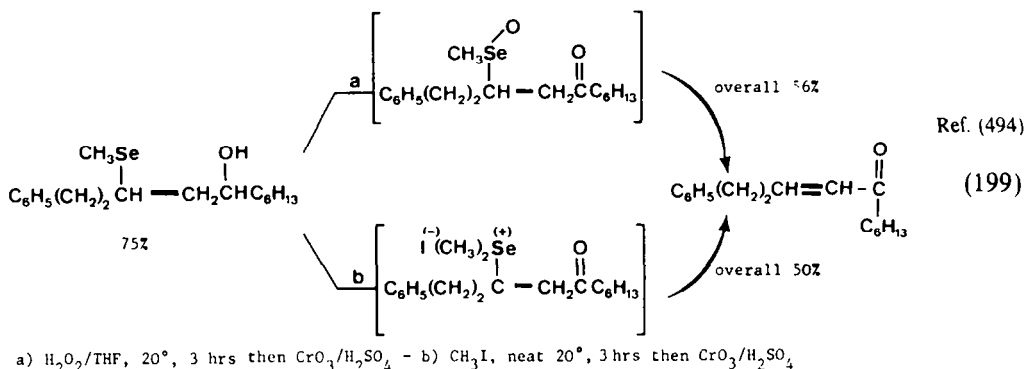


The high specificity of this synthesis is spectacular if one knows the different products which are expected under these reaction conditions (i.e. allyl alcohol, oxetanes, and ketones resulting from the C-C bond fragmentation<sup>494,524</sup>). An intramolecular reaction occurring via a 6-membered intermediate can explain this selectivity.<sup>494</sup> The obtention of both allyl and homoallyl alcohols from  $\gamma$ -hydroxyselenides and hydrogen peroxide in THF<sup>494</sup> further supports the previous explanation.

(b) We were however able in some instances to selectively prepare allyl alcohols<sup>279</sup> unavailable by other routes by transformation of the  $\gamma$ -hydroxyselenides to the  $\gamma$ -hydroxyalkylhalide (Chapter IIIC2) which are further reacted with MgO in HMPT (method AQ) (Eq. (197): 1  $\rightarrow$  4  $\rightarrow$  6).

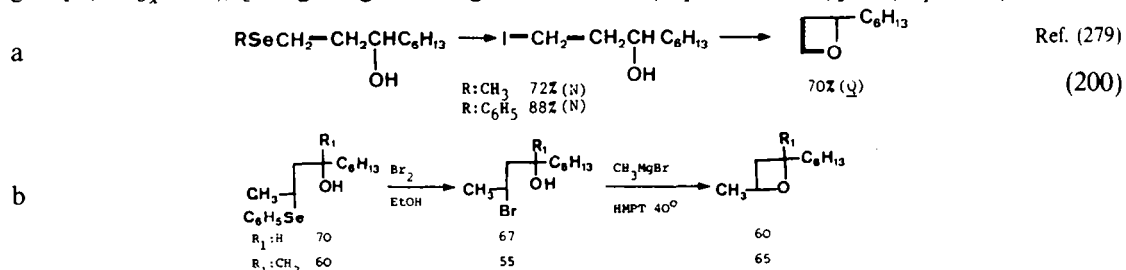
Again the selectively observed can be explained by a cyclic intramolecular transition state which takes advantage of a possible reaction between the OH group and magnesium oxide to produce the corresponding magnesium alcoholate.

(c) The specific synthesis of  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>494</sup> was directly achieved by reacting  $\gamma$ -hydroxyselenides with Jones reagent ( $\text{CrO}_3/\text{H}_2\text{SO}_4$ ,  $0^\circ$ , 3 hr;  $25^\circ$ , 24 hr) (Eq. 197, 199). This suggests that the hydroxyl group is oxidized prior the selenoxide elimination to direct the elimination toward the hydrogen  $\alpha$  to the carbonyl group which becomes the more acidic.<sup>494</sup> Another synthesis of  $\alpha$ -enones was achieved<sup>494</sup> in two steps by oxidation of the first formed  $\gamma$ -hydroxyselenonium salt (Eq. 199).



(d) Oxetanes have been prepared from  $\gamma$ -hydroxyselenides but this transformation is limited, at present, to specific cases. The hydroxyselenonium salt route was unsuccessful for this purpose since homoallyl alcohols are usually formed in high yield on treatment with base<sup>492</sup> (Chapter IIIC5a). In the cases where this is not possible or when the conditions (solvent base) are the most favourable for a substitution reaction, this occurs on the methyl group of the selenonium salt leading to  $\gamma$ -methoxyselenides.<sup>279</sup>

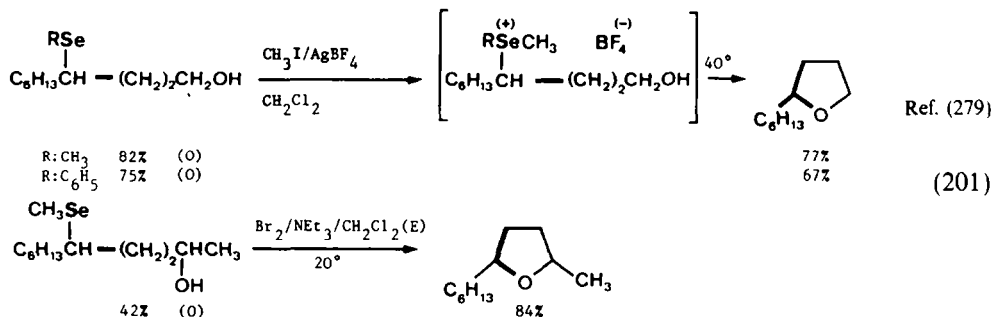
$\gamma$ -Hydroxyalkylhalides easily prepared from  $\gamma$ -hydroxyselenides (Chapter IIIC2) are transformed to oxetanes<sup>279</sup> in high yield when the halogen atom is attached to a primary carbon atom [(performed with *t*-BuOK in DMSO (Eq. 200)] or a secondary carbon atom exclusively attached to a methyl group ( $\text{CH}_3\text{xCH-}$ ), [using Grignard reagent in HMPT (Eq. 197: 4  $\rightarrow$  3)] or (Eq. 200b).



Use of *t*-BuOK in DMSO in place of  $\text{RMgX-HMPT}$  leads exclusively to the homoallyl alcohol (Eq. 197: 4  $\rightarrow$  3). This is also the case when the C atom bearing the halogen is attached to an Et group or a higher homologue ( $\text{C}_2\text{H}_5\text{xCH-}$ ) even when  $\text{RMgX-HMPT}$  is used.<sup>279</sup>

### IIIC6 Synthesis of furanes from $\delta$ -hydroxyselenides

$\delta$ -Hydroxyselenides derived from  $\alpha$ -selenoalkyllithiums and oxetane are easily transformed to tetrahydrofuranes. The reaction is cleaner under acidic than basic conditions.<sup>279</sup> This is achieved by heating the corresponding selenonium salts at  $40^\circ$  (Eq. 201) or directly by addition of bromine in ethanol/water or bromine in triethylamine on the  $\delta$ -hydroxyselenides<sup>279</sup> (Eq. 201).



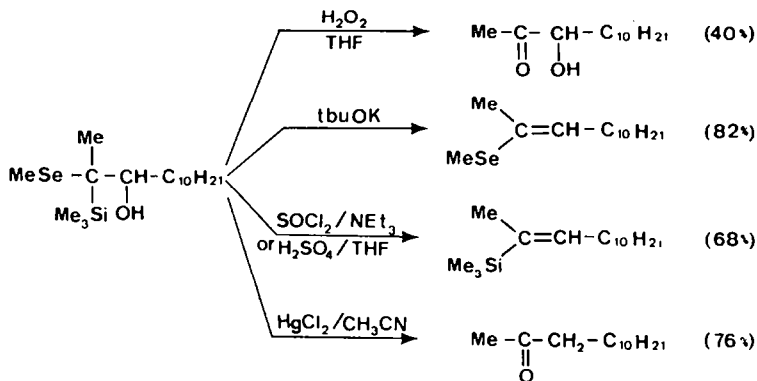
## CONCLUSIONS

$\alpha$ -Selenoalkyllithiums are valuable building blocks in organic synthesis. They are easily prepared from readily available and easily handled selenoacetals and ketals. Particularly important is the generality of the reaction of alkylolithiums on selenoacetals and ketals which allows the synthesis of a large variety of selenoalkyllithiums even those bearing two alkyl groups on the carbanionic center. They are stable at the temperature usually required for their further reaction with electrophiles.

Particularly valuable is the high nucleophilicity of these species, even the uncumbered ones, especially toward carbonyl compounds.

The selenides functionalized or not, obtained from  $\alpha$ -selenoalkyllithiums are stable derivatives which bear the selenyl moiety as a latent functionality. They have been selectively transformed on reaction with specific reagents to a large variety of selenium free derivatives including: alkanes, alkylhalides, alcohols, halogenoalcohols, allyl and homoallyl alcohols, olefins and dienes, carbonyl compounds including cyclobutanones and  $\alpha,\beta$ -unsaturated aldehydes, ketones and esters; epoxides including the  $\alpha,\beta$ -unsaturated ones, oxetanes and furanes. All these derivatives are prepared with concomitant new C-C bond formation.

The concept presented above can be extended to other derivatives and this is actually under investigation. We have gathered in the following scheme (Eq. 202) some transformations we have done on closely related  $\beta$ -hydroxy  $\alpha$ -silylselenides prepared from  $\alpha$ -lithio  $\alpha$ -silylselenides.<sup>115</sup>



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