Pure Appl. Chem., Vol. 75, No. 10, pp. 1453–1475, 2003.

Ring opening of heterocycles by an arene-catalyzed lithiation*,‡

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Abstract: The ring opening of different three-, four-, five- and six-membered oxygen-, nitrogen- and sulfur-containing saturated heterocycles using lithium and a catalytic amount of an arene (naphthalene or DTBB) yields a series of functionalized organolithium compounds, which, by reaction with different electrophiles, allow the preparation of polyfunctionalized molecules in only one synthetic operation.

INTRODUCTION

In a general context, the progress in organic synthesis is based on two important pillars: (a) The development of new synthetic strategies, that is, on paper how to go from a starting material to the desired target molecule (also considered as the retrosynthetic analysis) [1] and (b) the development of new methodologies, that is, how to perform in the lab what the chemist imagined before [2]. Concerning the second point, we have been interested in the last several years in the study of functionalized organometallic compounds because in their reaction with electrophiles they are able to yield polyfunctionalized molecules in only one reaction step [3]. Among the different possibilities, we have studied mainly functionalized organolithium intermediates due to their high reactivity, even at low temperatures, based on the high polarity of the carbon–lithium bond [4]. Thus, functionalized organolithium compounds have been used extensively in our group to prepare a wide series of functionalized structures, many of them taking part in naturally occurring biologically active products [5]. One inherent problem associated with the generation of very unstable organolithium compounds is that in some cases, this process has to be performed at low temperatures, so a very potent lithiation agent is necessary to be used. About 10 years ago, we found out that the combination of an excess of lithium powder and a catalytic amount of an arene, mainly naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB), is a versatile and efficient mixture to carry out lithiation reactions under very mild reaction conditions [6–9]. Thus, we were able to perform new processes, such as the preparation of organolithium reagents starting from nonhalogenated materials [10], the generation of dilithio synthons [11], the activation of metals [12] (especially nickel [13] or copper [14] and their use in reduction processes), and the preparation of functionalized organolithium compounds [5]. Concerning this last group of compounds, the most important methodology to prepare them involves a halogen–lithium exchange. However, in the last few years we have been applying the above-mentioned arene-catalyzed lithiation procedure to synthesize functionalized organolithiums starting from heterocyclic materials [5c], which is the subject of this paper.

*Lecture presented at the 4th Florida Heterocyclic Conference, Gainesville, FL, USA, 10–12 March 2003. Other presentations are published in this issue, pp. 1403–1475.

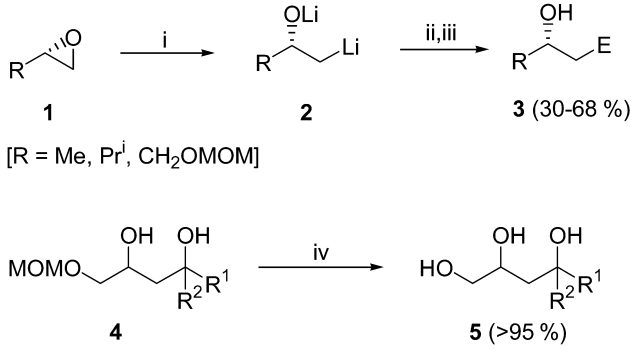
‡This paper is dedicated to Prof. A. R. Katritzky on the occasion of his 75th birthday.

THREE-MEMBERED HETEROCYCLES

The normal reactivity of three-membered rings is their ring opening with nucleophiles. In this section, we will show the umpolung [15] version of this process, which is the introduction of an electrophilic fragment at the less-substituted position of the heterocycle, through the corresponding organolithium intermediate.

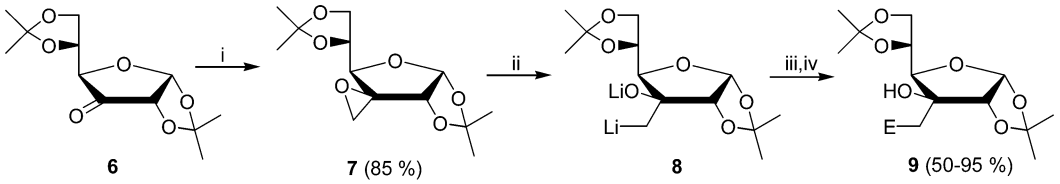
Epoxides

The reaction of chiral epoxides **1** with lithium and a catalytic amount of DTBB in THF at –78 °C led to the corresponding β-functionalized organolithium intermediate **2**, which, by treatment with different electrophiles at temperatures ranging between –78 °C and room temperature, led, after hydrolysis with water, to the expected chiral products **3** in a regioselective manner (Scheme 1) [16]. In the case of using prostereogenic carbonyl compounds as electrophiles, an almost 1:1 mixture of diastereomers was isolated, which was separated by column chromatography. When the starting material was the enantiomeric epoxide (*ent*-**1**) the corresponding series of products *ent*-**3** were isolated. On the other hand, hydrolysis of compounds **4** (resulting from the use of the starting MOMO-epoxide and a carbonyl compound as electrophile) with hydrochloric acid in methanol gave differently substituted triols **5** (Scheme 1).



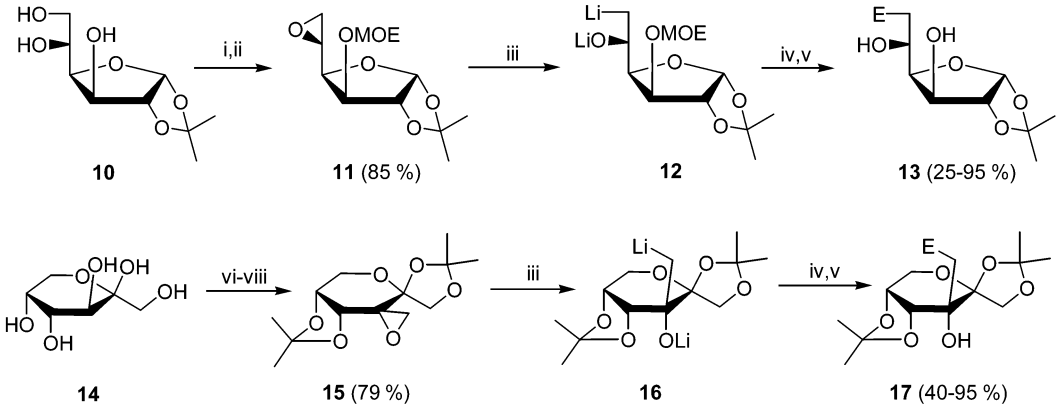
Scheme 1 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –78 °C; (ii) E^+ = H_2O, D_2O, Bu^{t}CHO, PhCHO, $(CH_2)_5CO$, PhCOMe, CO_2, –78 °C to rt; (iii) H_2O; (iv) HCl, MeOH.

The methodology shown in Scheme 1 was applied to the synthesis of the so-called functionalized branched carbohydrates, which are glycosidic components of many antibiotics [17]. Thus, the successive reaction of the glucose epoxide derivative **7** (easily prepared from the corresponding ketone **6**) with lithium and a catalytic amount of DTBB, and an electrophile yielded, under the conditions aforementioned, the expected products **9** in a regio- and stereoselective manner, the corresponding lithium intermediate **8**, being involved in the process (Scheme 2) [18].



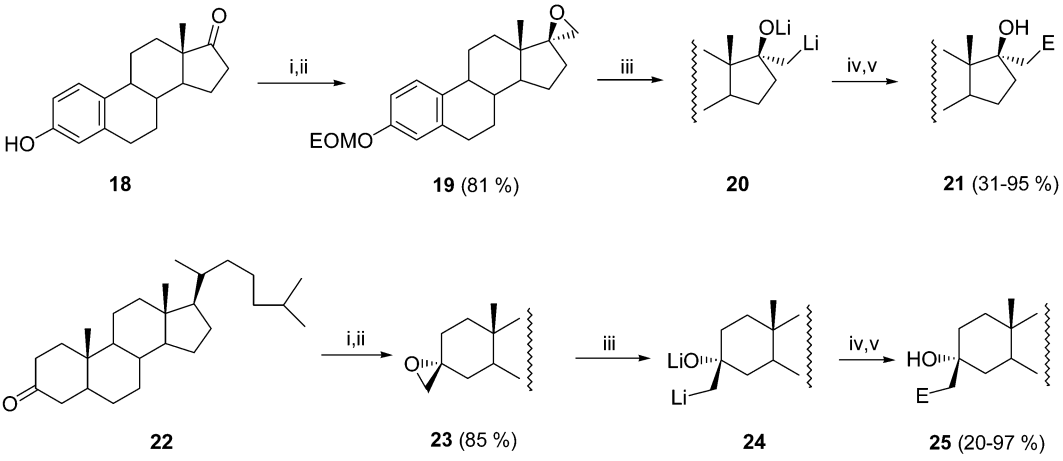
Scheme 2 *Reagents and conditions*: (i) $[Me_3SO]I$, Bu^{t}OK, Bu^{t}OH, 50 °C; (ii) Li, DTBB (5 %), –78 °C, 2 h; (iii) E^+ = H_2O, D_2O, Me_3SiCl, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, –78 °C; (iv) H_2O, –78 °C to rt.

The application of the same methodology to the epoxides **11** and **15** [easily prepared from glucose (**10**) and fructose (**14**) derivatives, respectively], generated intermediates **12** and **16**, and final products **13** and **17**, respectively (Scheme 3) [18]. This chemistry is also applicable to the preparation of methylenic-bridged disaccharides by using, for instance, intermediate **16** and the ketone precursor of epoxide **15**, the obtained yields being low due to decomposition of the product in the final chromatographic purification [18].



Scheme 3 *Reagents and conditions*: (i) PPh_3, DIAD, benzene, reflux; (ii) Bu^nLi, then $EtOCH_2Cl$, –78 °C to rt; (iii) Li, DTBB (5 %), –78 °C; (iv) $E^+ = H_2O$, D_2O, PhCHO, Me_2CO, $(CH_2)_5CO$, CO_2, –78 °C to rt; (v) H_2O; (vi) $Me_2C(OMe)_2$, $HClO_4$ cat., Me_2CO, 0 °C; (vii) PCC, Ac_2O, CH_2Cl_2; (viii) $[Me_3SO]I$, $KOBu^t$, Bu^tOH, 50 °C.

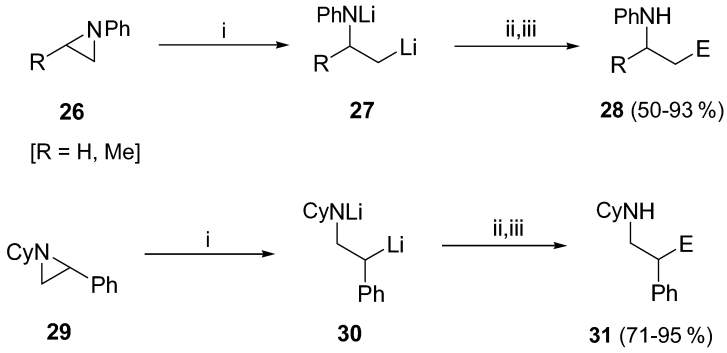
Epoxy esteroids **19** and **23** were easily prepared from estrone (**18**) and cholestanone (**22**), respectively. Their DTBB-catalyzed lithiation and reaction with different electrophiles, under the above-mentioned reaction conditions, yielded compounds **21** and **25**, involving the corresponding intermediates **20** and **24**, respectively (Scheme 4) [19].



Scheme 4 *Reagents and conditions*: (i) Bu^nLi, then $EtOCH_2Cl$, –78 °C; (ii) $[Me_3SO]I$, $KOBu^t$, Bu^tOH, 50 °C; (iii) Li, DTBB (5 %), –78 °C; (iv) $E^+ = H_2O$, D_2O, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, CO_2, –78 °C to rt; (v) H_2O, –78 °C to rt.

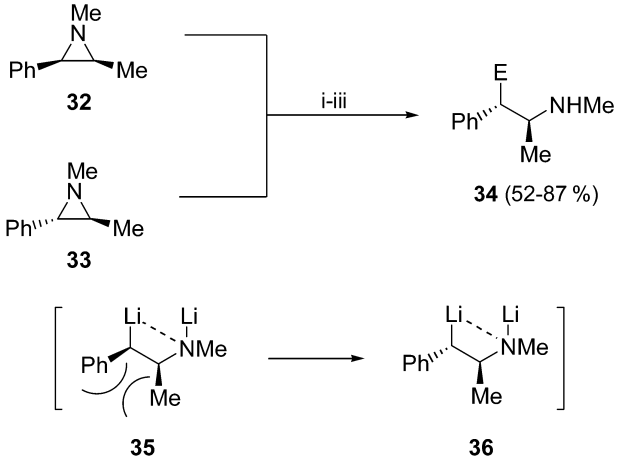
Aziridines

Aziridines can be opened using an arene-catalyzed lithiation only if an aryl group is attached to one of the atoms of the ring. For *N*-phenylaziridines **26**, their reaction with an excess of lithium and a catalytic amount of naphthalene in THF at –78 °C followed by condensation of the intermediate **27** with an electrophile afforded, after hydrolysis with water, the expected functionalized amines **28** in a regioselective manner (Scheme 5). When the phenyl group is attached to one of the carbon atoms of the ring, such as in the starting material **29**, the benzylic organolithium intermediate **30** is the most stable one generated, which by successive reaction with an electrophile and final hydrolysis with water gave products **31** (Scheme 5) [20].



Scheme 5 *Reagents and conditions*: (i) Li, $C_{10}H_8$ (5 %), THF, –78 °C; (ii) E^+ = H_2O, D_2O, MeI, CH_2=$CHCH_2Br$, Me_2S_2, Bu^{t}CHO, PhCHO, Me_2CO, $(CH_2)_5CO$, $(EtO)_2CO$, CH_2=$CHCO_2Me$, $PhCON(CH_2)_4$, PhCH=NPh, –78 °C to rt; (iii) H_2O.

Surprisingly, when chiral *cis*- (**32**) and *trans*-aziridine (**33**) [easily prepared from (–)-ephedrine] were submitted to the same protocol as for aziridines **26** or **29**, the same products **34** were isolated. In this case, starting from the cis starting material, the generated intermediate **35** has a rather rigid structure due to the so-called CIPE (complex induced complexity effect) [21], which implies a strong interaction between the heteroatom and the lithium atom and consequently an important steric hindrance. For this reason, it suffers a benzylic inversion [22], giving the epimeric intermediate **36**, the same gen-

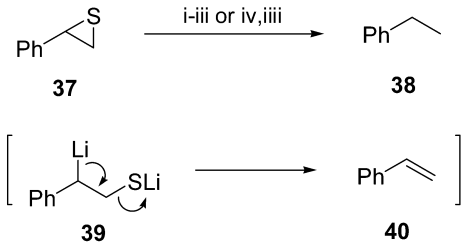


Scheme 6 *Reagents and condition*: (i) Li, $C_{10}H_8$ (5 %), THF, –78 °C; (ii) E^+ = H_2O, D_2O, CH_2=$CHCH_2Br$, Me_2CO, $(c\text{-}C_3H_5)_2CO$, –78 °C to rt; (iii) H_2O.

erated by ring opening from the *trans*-aziridine **33**, so the final products are the same in both cases (Scheme 6) [20].

Thiiranes

The lithiation of phenylthiirane **37** was performed using a catalytic amount of DTBB under the above-mentioned reaction conditions or in the presence of the electrophile (Barbier-type reaction conditions) [23], but incorporation of the electrophile was never observed, ethylbenzene (**38**) being the only reaction product obtained [24]. Probably, the ring opening takes place at the most stable benzylic position giving the intermediate **39**, but then a β-elimination occurs (lithium sulfide is a good leaving group) yielding styrene (**40**), which in the final work-up suffers reduction (with the excess of lithium and water used in the final hydrolysis) affording ethylbenzene (Scheme 7).



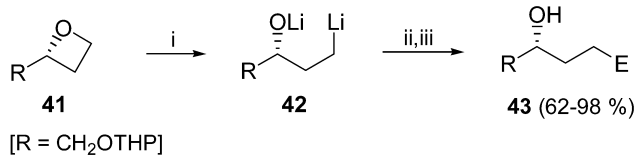
Scheme 7 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –78 °C; (ii) $E^+ = R_2CO$, R_3SiCl, –78 °C to rt; (iii) H_2O; (iv) Li, DTBB (5 %), $E^+ = R_2CO$, R_3SiCl, THF, –78 °C to rt.

FOUR-MEMBERED HETEROCYCLES

The reductive ring opening of four-membered heterocycles allows the introduction of a functionalized four-carbon unit into electrophiles.

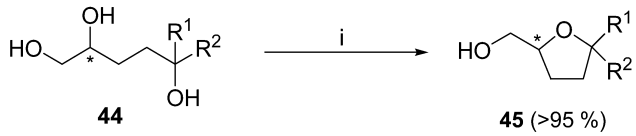
Oxetanes

Lithiation of the chiral oxetane **41** in the presence of a catalytic amount of DTBB in THF at –78 °C led to the γ-functionalized organolithium intermediate **42**, which by reaction with different electrophiles afforded, after hydrolysis with water, the expected functionalized alcohols **43** (Scheme 8) [25]. Starting from the enantiomeric oxetane *ent*-**41**, the corresponding enantiomeric products *ent*-**43** were prepared. When a prochiral carbonyl compound was used as electrophile a ca. 1:1 mixture of diastereomers was obtained, which could be separated by column chromatography.



Scheme 8 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –78 °C; (ii) $E^+ = H_2O$, D_2O, Bu′CHO, PhCHO, Me_2CO, $(CH_2)_4CO$, CO_2, –78 °C to rt; (iii) H_2O.

Scheme 9 shows the cyclization of compounds **44** [resulting from the reaction of intermediates **42** (or *ent*-**42**) with carbonyl compounds R^1R^2CO] with *p*-toluenesulfonic acid in methanol to give the corresponding homochiral tetrahydrofurans **45**.

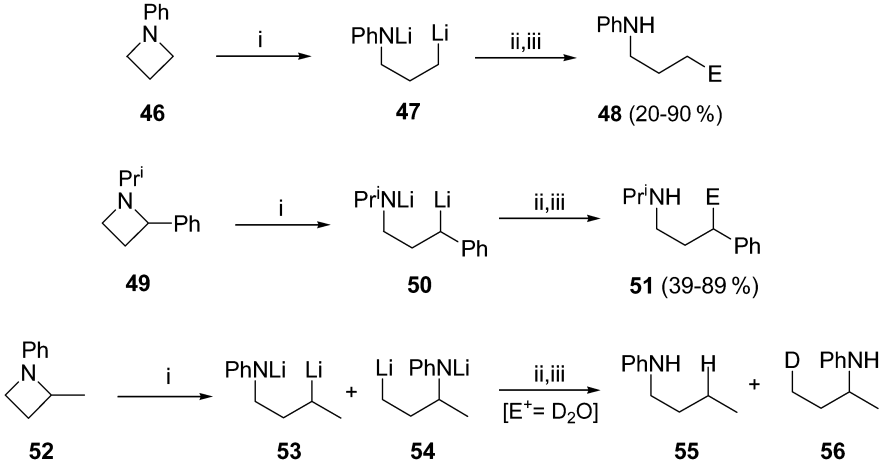


44 **45** (>95 %)

Scheme 9 *Reagents and conditions*: (i) *p*-$MeC_6H_4SO_3H$, MeOH.

Azetidines

The ring opening of azetidines with lithium and a catalytic amount of DTBB has to be carried out at higher temperatures than for aziridines, needing also here the presence of a phenyl group either at the nitrogen atom or at the adjacent position. Thus, *N*-phenylazetidine (**46**) was opened with lithium and DTBB as the catalyst in THF at –15 °C yielding the corresponding γ-functionalized organolithium compound **47**, which upon treatment with different electrophiles gave, after hydrolysis with water, the expected functionalized amines **48** (Scheme 10) [26]. The same protocol applied to the azetidine **49** took place, giving the most stable benzylic intermediate **50**, which after condensation with an electrophile gave products **51**. However, the process with the azetidine **52** gave a 2:1 mixture of products **55** and **56**, after quenching with deuterium oxide of the corresponding intermediates **53** and **54**. As shown, in the case of the secondary organolithium compound **53**, no deuterium incorporation was observed, because this intermediate abstract a proton from the reaction medium [27] before reacting with the electrophile under the reaction conditions assayed.



46 **47** **48** (20-90 %)

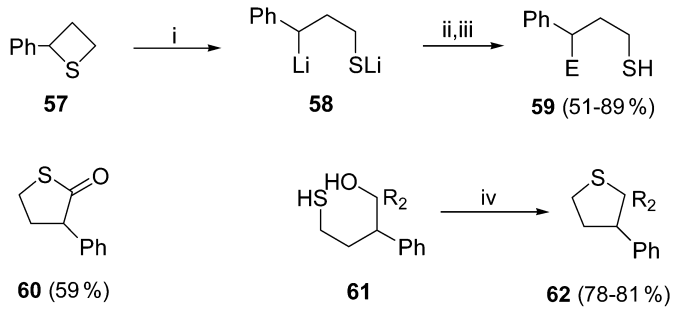
49 **50** **51** (39-89 %)

52 **53** **54** **55** **56**

Scheme 10 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –15 °C; (ii) E^+ = H_2O, D_2O, CH_2=$CHCH_2Br$, Bu^tCHO, PhCHO, Me_2CO, $(CH_2)_5CO$, PhCH=NPh, CO_2, –15 °C to rt; (iii) H_2O.

Thietanes

2-Phenylthietane (**57**) was opened with lithium and a catalytic amount of DTBB in THF at –78 °C to give the intermediate **58**, which by treatment with an electrophile gave, after hydrolysis with water, products **59** (Scheme 11) [28]. When carbon dioxide was used as electrophile, the corresponding thiolactone **60** was isolated after work-up. In addition, products **61**, resulting from the reaction of intermediate **58** with carbonyl compounds, were cyclized to substituted thiophenes **62** under acidic conditions.



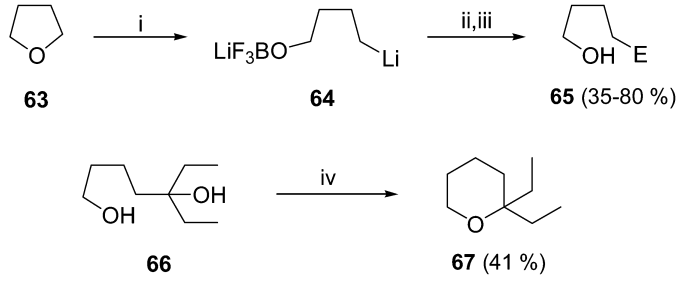
Scheme 11 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –78 °C; (ii) $E^+ = D_2O$, Me_3SiCl, Pr^iCHO, Bu^tCHO, PhCHO, Me_2CO, Et_2CO, Pr^nCOMe, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe, CO_2, –78 °C to rt; (iii) H_2O; (iv) 85 % H_3PO_4, PhMe reflux.

FIVE-MEMBERED HETEROCYCLES

The ring opening of five-membered heterocycles allows the introduction of a functionalized five-carbon chain into electrophilic reagents.

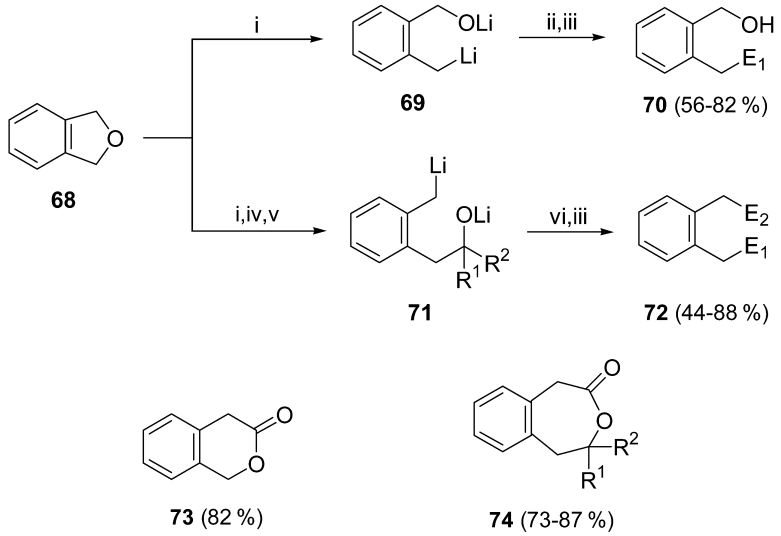
Oxygen-containing heterocycles

Tetrahydrofuran (**63**) itself can be opened using the arene-catalyzed technology, but boron trifluoride is needed for the reaction to take place. As electron carriers naphthalene, biphenyl (B) or DTBB can be used at –78 °C, so intermediate **64** was postulated to react with the electrophile giving, after hydrolysis with water, the expected functionalized alcohols **65** (Scheme 12) [29]. Diols resulting from the reaction of intermediate **64** with carbonyl compounds can be easily cyclized to the corresponding tetrahydropyrans. For instance, treatment of compound **66** with 85 % phosphoric acid under toluene reflux gave the heterocycle **67**, the whole process **63** → **67** being a homologation of the starting material.



Scheme 12 *Reagents and conditions*: (i) Li, $C_{10}H_8$, B or DTBB (5 %), THF, $BF_3{\cdot}OEt_2$, –78 °C; (ii) Pr^iCHO, Bu^nCHO, Bu^tCHO, PhCHO, Et_2CO, Bu^tCOMe, PhCOMe, –78 °C to rt; (iii) H_2O; (iv) 85 % H_3PO_4, PhMe reflux.

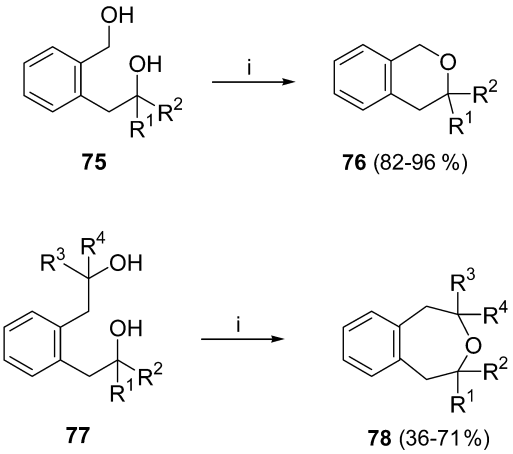
In the case of phthalan (**68**), its DTBB-catalyzed lithiation in THF took place at room temperature giving intermediate **69**, which reacted with different electrophiles to yield, after hydrolysis with water, the corresponding products **70** (Scheme 13) [30]. An interesting reaction occurred when, after the reaction with the first carbonyl compound as electrophile (E_1^+), the temperature was allowed to rise to room temperature, so in the presence of the excess of lithium a second lithiation afforded the second intermediate **71**, which, by condensation with another electrophile (E_2^+), gave, after final hydrolysis with water, the expected products **72**, in which two different electrophilic fragments have been introduced in the molecule of the starting material. When carbon dioxide was used as the first electrophile,



Scheme 13 *Reagents and conditions*: (i) Li, DTBB (2.5 %), THF, rt; (ii) E_1^+ = D_2O, CO_2, Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, PhCOMe, –78 °C; (iii) H_2O, –78 °C to rt; (iv) E_1^+ = EtCHO, Pr^{i}CHO, Bu^{t}CHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCH=NPh, –78 °C; (v) rt; (vi) E_2^+ = H_2O, D_2O, CO_2, EtCHO, Bu^{t}CHO, PhCHO, Et_2CO, $(CH_2)_5CO$, –78 °C to rt.

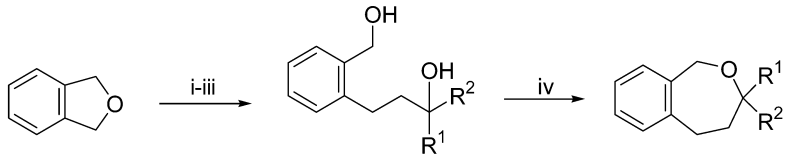
after hydrolysis, the corresponding lactone **73** was directly isolated. In addition, using first a carbonyl compound and then carbon dioxide, a series of seven-membered lactones **74** were obtained.

Diols **75** (of type **70**, from a carbonyl compound as electrophile) or **77** (of type **72**, from two different carbonyl compounds as electrophiles) can be easily cyclized using 85 % phosphoric acid under toluene reflux to give heterocycles **76** and **78**, respectively. Considering the transformation of phthalan into compounds **76** and **78**, it can be considered as a homo- and bishomologation of the starting material, respectively.



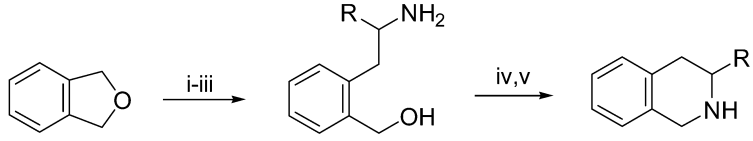
Scheme 14 *Reagents and conditions*: (i) 85 % H_3PO_4, PhMe reflux.

The reaction of intermediate **69** (see Scheme 13), generated from phthalan (**68**), with epoxides afforded, after hydrolysis with water, the expected diols **79** (Scheme 15) [31]. Boron trifluoride-promoted cyclization of these diols gave the corresponding seven-membered heterocycles **80**.



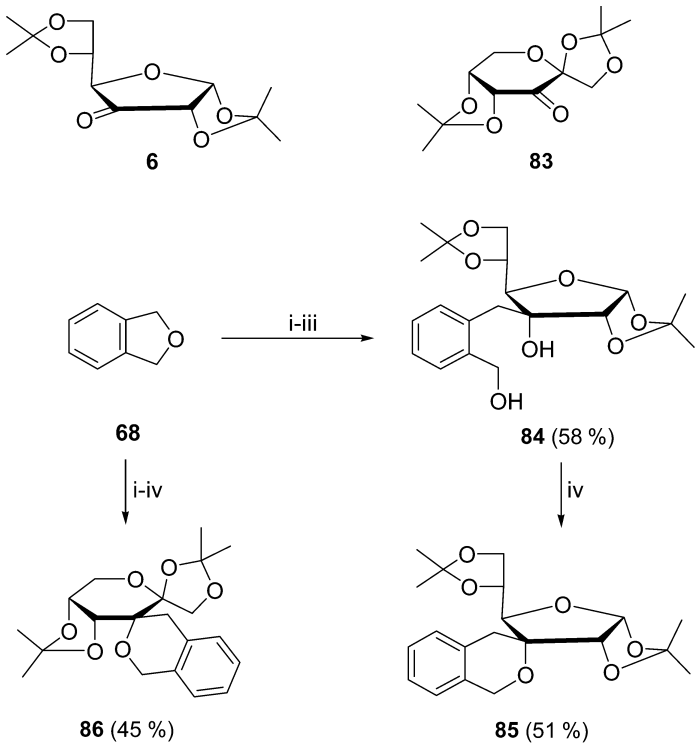
Scheme 15 *Reagents and conditions*: (i) Li, DTBB (2.5 %), THF, 0 °C; (ii) $R^1R^2C(O)CH_2$ = $MeCH(O)CH_2$, n-$C_6H_{13}CH(O)CH_2$, $(CH_2)_7C(O)CH_2$, $PhCH(O)CH_2$, THF, 0 °C; (iii) H_2O, 0 °C to rt; (iv) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –30 °C to rt.

Once intermediate **69** was generated and the excess of lithium was removed by filtration, it was allowed to react with *N*-silylimines at temperatures between –45 °C and room temperature, so the corresponding amino alcohols **81** were isolated, after hydrolysis with water (Scheme 16) [32]. Successive treatment of compounds **81** with thionyl chloride and sodium hydroxide gave tetrahydroisoquinolines **82**.



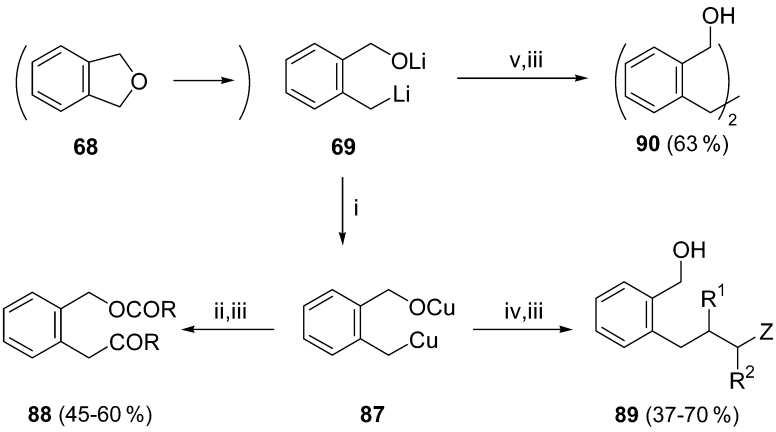
Scheme 16 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, 0 °C, then filtration; (ii) $RCH{=}NSiMe_3$ (R = Bu^t, Ph, 2-furyl), –45 °C to rt; (iii) H_2O; (iv) $SOCl_2$, $CHCl_3$; (v) 5 M NaOH.

The use of more sophisticated electrophiles such as ketones **6** and **83** allows the preparation of carbohydrates containing a heterocyclic moiety. Thus, using intermediate **69** and the glucose derivative **6**, diol **84** was isolated after hydrolysis with water (Scheme 17), its easy cyclization under Mitsunobu type reaction conditions giving the expected compound **85**. The same process can be carried out without isolation of the diol intermediate, as the preparation of the fructose derivative **86** illustrates, using in this case ketone **83** as the corresponding electrophile [18].

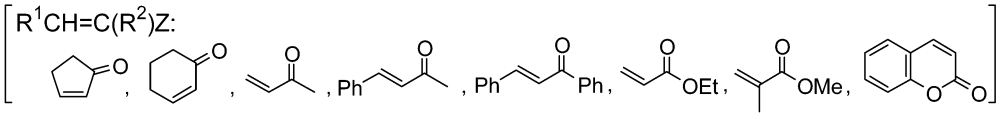


Scheme 17 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, 0 °C; (ii) ketone **6** or **83**, –78 °C to rt; (iii) H_2O; (iv) PPh_3, DIAD, PhH reflux.

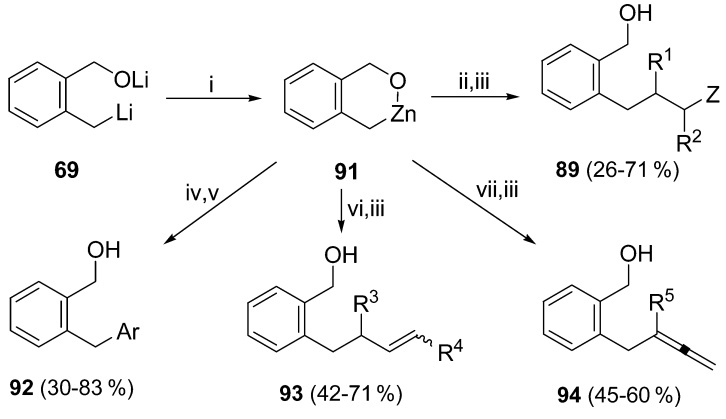
As it is well known in lithium chemistry, there are some reactions that result problematic with organolithiums, such as conjugate addition or acylation, due to competitive 1,2-additon or over-addition, respectively [4]. Moreover, dimerization of sp^3-hybridized organolithium has also problems due to reduction side-processes. One way to overcome these problems is to exchange lithium by other less-reactive metals. Thus, once the functionalized organolithium compound **69** was generated from phthalan (**68**), a lithium–copper transmetalation was carried out using a copper(I) halide at –78 °C, so a new intermediate of type **87** was formed in situ, which now can be used to give conjugate addition to α,β-unsaturated carbonyl compounds and esters to yield, after hydrolysis, the expected products **89** (Scheme 18). The acylation of intermediate **87** with acyl chlorides afforded acylated ketones **88**. In addition, treatment of intermediate **69** with copper(II) chloride gave cleanly diol **90** [33].



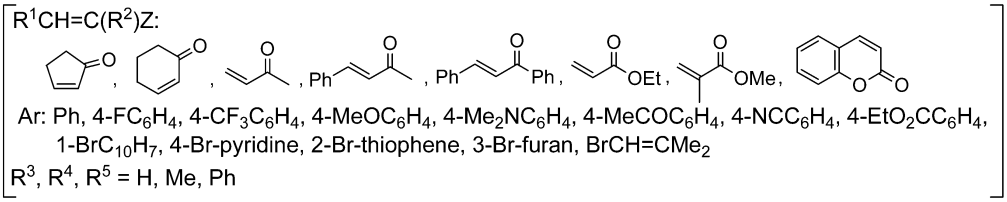
Scheme 18 *Reagents and conditions*: (i) CuX (X = Br, I), THF, –78 °C; (ii) $R^1CH{=}C(R^2)Z$, –78 °C; (iii) NH_4Cl–H_2O, –78 °C to rt; (iv) RCOCl (R = Bu^t, Ph), –78 °C; (v) $CuCl_2$, THF, –78 °C.



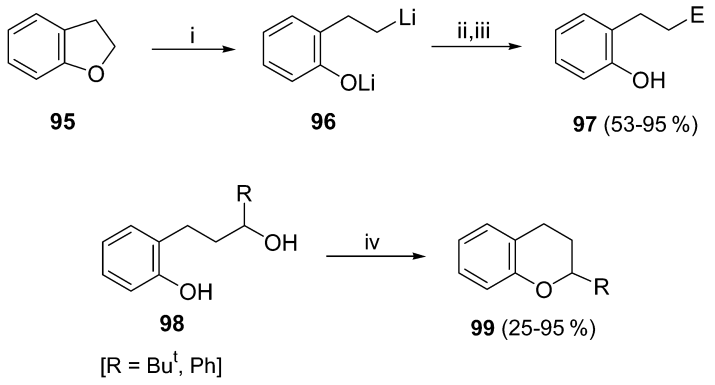
A similar chemistry was carried out using a lithium–zinc transmetalation from the intermediate **69**, which, by treatment with a zinc halide, gave an organozinc intermediate of type **91**. Further reaction of this new system with electrophilic olefins gave the same compounds **89** as using the copper methodology [34]. New reactions in the case of using intermediate **91** are the palladium-catalyzed Negishi coupling with aryl bromides to afford compounds **92** [35] and the copper(I) catalyzed S_N2' reaction with allylic or propargylic bromides giving compounds **93** and **94**, respectively [36] (Scheme 19).



Scheme 19 *Reagents and conditions*: (i) ZnX_2 (X = Cl, Br, I), THF, –78 °C; (ii) $R^1CH{=}C(R^2)Z$, –78 °C; (iii) NH_4Cl–H_2O, –78 °C to rt; (iv) ArBr, $Pd(PPh_3)_4$ (5 %), 60 °C; (v) HCl–H_2O; (vi) $R^3CH{=}CHCH(R^4)Br$, CuCN; (vii) $R^5C{\equiv}CCH_2Br$, CuCN.

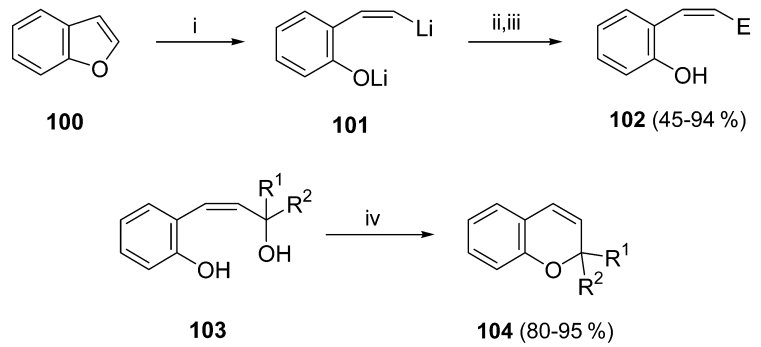


The DTBB-catalyzed lithiation of 2,3-dihydrobenzofuran (**95**) in THF at room temperature led to the formation of intermediate **96**, resulting from a benzylic-type carbon–oxygen cleavage, which, by reaction with different electrophiles, gave functionalized phenols **97** (Scheme 20) [37]. Some aldehyde derivatives (**98**) were cyclized under Mitsunobu-type reaction conditions to yield products **99**, homologs of the starting material.



Scheme 20 *Reagents and conditions*: (i) Li, DTBB (5 %), THF; (ii) E^+ = H_2O, D_2O, Me_3SiCl, Bu^{t}CHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, –40 °C to rt; (iii) H_2O; (iv) PPh_3, DIAD, PhH reflux.

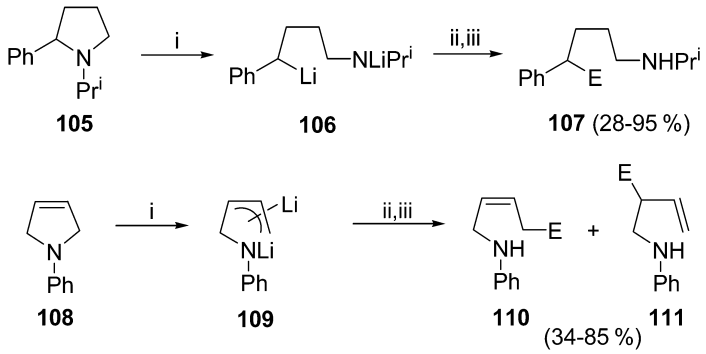
More interesting, from a stereochemical point of view, is the reductive ring opening of 2,3-benzofuran (**100**). In this case, the reaction with lithium and a catalytic amount of DTBB in THF at 0 °C led to the intermediate **101** in which the geometry of the carbon–carbon double bond is kept. Its reaction with electrophiles gave the final products **102**, having a cis configuration (Scheme 21) [38]. Compounds **103** (of type **102**, resulting from the use of carbonyl compounds as electrophiles) can be easily cyclized under acidic conditions (85 % H_3PO_4 or $ZnCl_2$) to give the corresponding chromenes **104**.



Scheme 21 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, 0 °C; (ii) E^+ = H_2O, D_2O, Bu^{t}CHO, PhCHO, $Ph(CH_2)_2CHO$, Me_2CO, Pr^{n}COMe, PhCOMe, $(CH_2)_4CO$, –78 °C; (iii) H_2O, –78 °C to rt; (iv) 85 % H_3PO_4, PhMe reflux or $ZnCl_2$, $ClCH_2CH_2Cl$.

Nitrogen-containing heterocycles

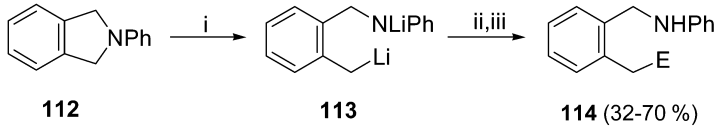
Whereas *N*-phenylpyrrolidine does not suffer reductive opening with lithium and a catalytic amount of DTBB, *N*-isopropyl-2-phenypyrrolidine (**105**) reacted with the mentioned mixture in THF at room temperature to give intermediate **106**, which was treated with different electrophiles to afford, after hydrolysis with water, the corresponding functionalyzed amines **107** (Scheme 22) [39]. When the same protocol was applied to *N*-phenylpyrroline **108**, the ring opening gave a delocalized allyllithium inter-



Scheme 22 *Reagents and conditions*: (i) Li, DTBB (2.5 %), THF, rt; (ii) $E^+ = H_2O$, D_2O, MeI, Bu^{t}CHO, PhCHO, Me_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, CO_2, –78 °C to rt; (iii) H_2O.

mediate **109**, which, by trapping with an electrophile, afforded a mixture of the corresponding products **110** and **111**, in different ratio depending on the electrophile used.

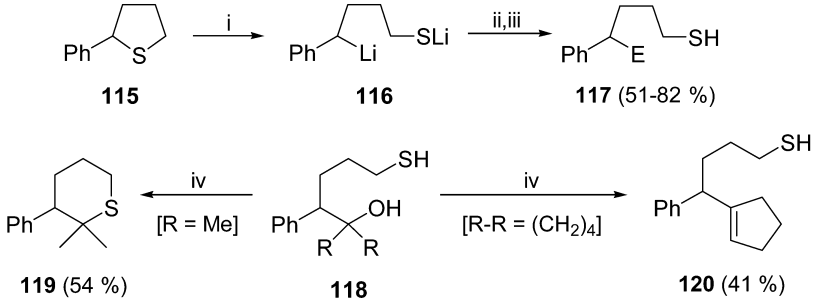
In the case of *N*-isopropylindoline, the DTBB-catalyzed lithiation failed, but for the corresponding *N*-phenyl derivative **112** the reductive opening took place in THF at room temperature, giving the functionalized organolithium intermediate **113**. After reaction with different electrophiles and final hydrolysis with water, functionalized amines **114** were isolated (Scheme 23) [39]. In this case, amino alcohols **114**, resulting from the reaction of intermediate **113** with carbonyl compounds, could not be cyclized under acidic conditions to the corresponding tetrahydroisoquinolines.



Scheme 23 *Reagents and conditions*: (i) Li, DTBB (4.5 %), THF; (ii) $E^+ = H_2O$, D_2O, Pr^{i}CHO, Bu^{t}CHO, PhCHO, Me_2CO, PhCOMe, –78 °C; (iii) H_2O, –78 °C to rt.

Sulfur-containing heterocycles

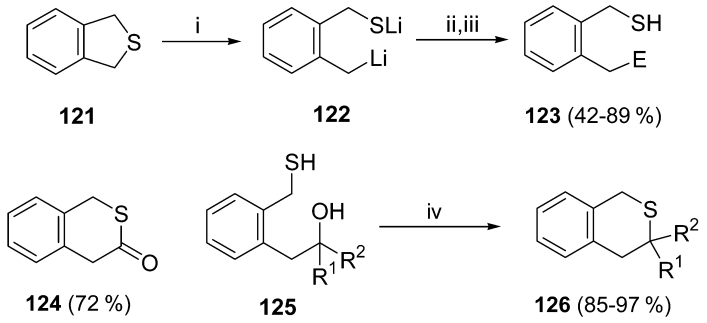
2-Phenyltetrahydrothiophene (**115**) reacted with lithium and a catalytic amount of DTBB in THF at –78 °C to give the intermediate **116**, which was trapped with several electrophiles at the same temperature to yield, after hydrolysis with water, functionalized thiols **117** (Scheme 24) [28]. For carbonyl compound derivatives **118**, the acidic treatment gave different behavior depending on the structure of



Scheme 24 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –78 °C; (ii) $E^+ = D_2O$, Bu^{t}CHO, Et_2CO, $(CH_2)_4CO$, CO_2, –78 °C; (iii) H_2O, –78 °C to rt; (iv) 85 % H_3PO_4, PhMe reflux.

the hydroxy thiol. For instance, whereas for R = Me, the corresponding six-membered ring **119** was obtained, the cyclopentanone derivative [R-R = $(CH_2)_4$] afforded exclusively the olefin **120**.

The reaction of thiophthalan (**121**) with lithium and a catalytic amount of DTBB in THF at –78 °C gave intermediate **122** and products **123**, after condensation with different electrophiles at the same temperature and final hydrolysis with water (Scheme 25) [40]. When carbon dioxide was used as electrophile, the corresponding thiolactone **124** was directly obtained after work-up. In addition, the employ of carbonyl compounds as electrophiles gave hydroxy thiols **125**, which were easily cyclized with 85 % H_3PO_4 to yield products **126**, which are homologs of the starting material **121**.



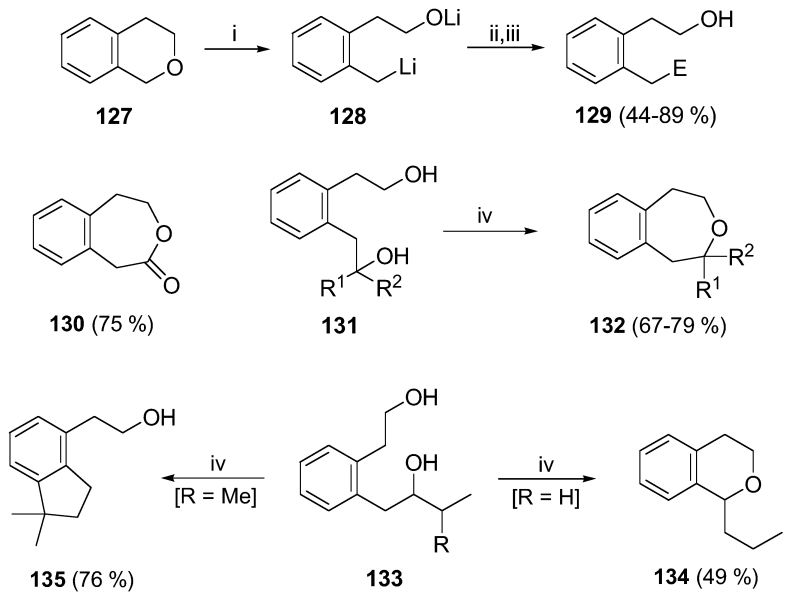
Scheme 25 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –78 °C; (ii) E^+ = H_2O, D_2O, Pr^iCHO, Bu^tCHO, PhCHO, $(CH_2)_4CO$, PhCOMe, CO_2, –78 °C; (iii) H_2O, –78 °C to rt; (iv) 85 % H_3PO_4, PhMe reflux.

SIX-MEMBERED HETEROCYCLES

The reductive ring opening of six-membered heterocycles is more difficult than in the case of smaller rings. As an example, tetrahydropyran does not suffer ring opening by an arene-catalyzed lithiation even in the presence of boron trifluoride, in contrast to the same process, which works for tetrahydrofuran (see previous section, "Oxygen-containing heterocycles").

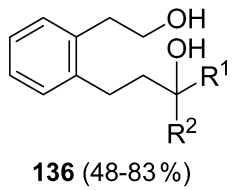
Oxygen-containing heterocycles

The reaction of isochroman (**127**) with lithium and a catalytic amount of DTBB in THF at room temperature led to the generation of intermediate **128**, which, after reacting with different electrophiles and final hydrolysis with water, gave the expected functionalized alcohols **129** (Scheme 26) [41]. When carbon dioxide was used as electrophile, the seven-membered lactone **130** was directly isolated after work-up. In addition, acidic treatment of diols **131** derived from ketones as electrophiles gave the expected seven-membered heterocycles **132**. For aldehyde derivatives **133**, the same treatment gave different results depending on the structure of the starting aldehyde: whereas the propanal-derived diol (**133**, R = H) gave the cyclic ether **134**, for the isobutyraldehyde-derived diol (**133**, R = Me) a Friedel–Craft reaction took place, giving the bicyclic compound **135**.



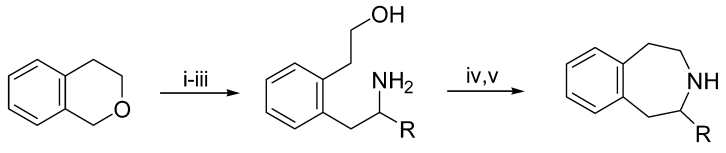
Scheme 26 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, rt; (ii) H_2O, D_2O, EtCHO, Pr^{i}CHO, Bu^{t}CHO, PhCHO, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, PhCOMe, –78 °C to rt; (iii) H_2O; (iv) 85 % H_3PO_4, PhMe reflux.

The reaction of intermediate **128** with epoxides [$R^1R^2C(O)CH_2$] under the conditions shown in Scheme 26 gave the corresponding diols **136**, which could not be cyclized under acidic conditions to yield the expected eight-membered benzofused cyclic ethers [31].



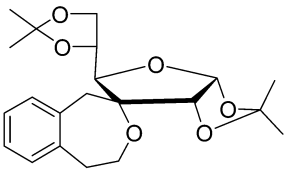
136 (48-83 %)

As mentioned before, for phthalan (**68**, Scheme 16), also in the case of isochroman (**127**), it was possible to use a silylated imine as electrophile to prepare the corresponding amino alcohols **137** and, after cyclization under the same reaction conditions, the expected seven-membered nitrogen-containing heterocycles **138** (Scheme 27) [32].

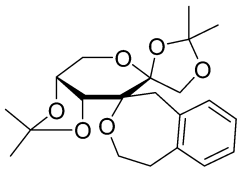


Scheme 27 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, 0 °C, then filtration; (ii) RCH=NSiMe$_3$ (R = Bu^t, Ph, 2-furyl), –45 °C to rt; (iii) H_2O; (iv) $SOCl_2$, $CHCl_3$; (v) NaOH.

When ketones **6** and **83** (see Scheme 17) were used as electrophiles with intermediate **128**, after the corresponding cyclization under Mitsunobu-type reaction conditions, the heterocyclic carbohydrates **139** and **140** were obtained, respectively [18].

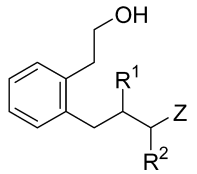


139 (70 %)

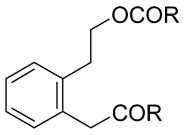


140 (41 %)

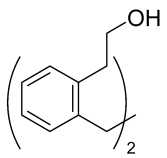
Finally, after transmetalation on intermediate **128** with a copper(I) or zinc halides, the corresponding new organocopper or organozinc species formed gave similar reactions as they were described for phthalan in Schemes 18 and 19. Thus, by reaction of both copper or zinc derivatives with electrophilic olefins yielded the expected conjugate addition leading to compounds **141** [33,34]. Acylation of the copper intermediate gave acyl ketones **142** [33]. Dimerization with copper(II) chloride gave diol **143** [33]. The zinc derivative could be arylated under palladium catalysis (Negishi reaction) to give diarylated alcohols **144** [35] or react with allylic or propargylic halides to undergo a S_N2' reaction affording compounds **145** and **146**, respectively [36].



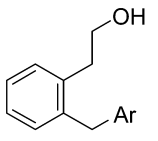
141 (26-75 %)



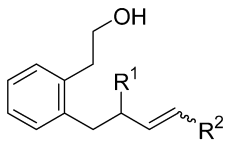
142 (35-65 %)



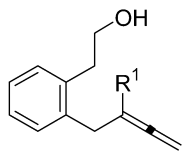
(**143** 59 %)



144 (30-78 %)

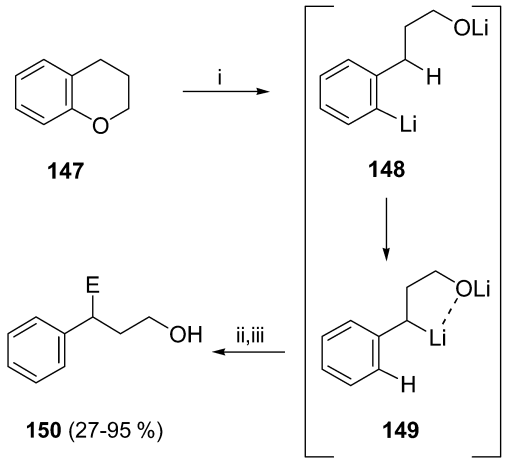


145 (49-63 %)



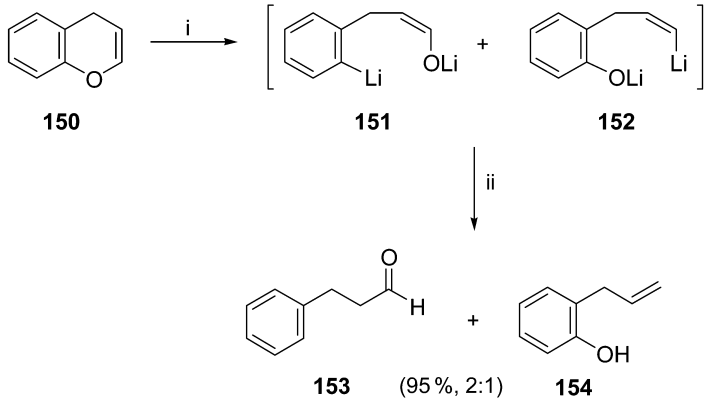
146 (49-60 %)

The DTBB-catalyzed lithiation of chroman (**147**) in THF at room temperature gave a surprising result, because after reacting with different electrophiles and final hydrolysis gave compounds **150** as the main products. It would mean that after the first ring opening by cleavage of the sp^2-carbon-oxygen bond, the initially formed intermediate **148** is transformed into the most stable (benzylic and chelated) one **149**, which is the real organolithium compound responsible of the structure in products **150** (Scheme 28) [42]. Products resulting from the reaction of intermediate **148** with the electrophile were detected in some cases with yields <10 %.



Scheme 28 *Reagents and conditions*: (i) Li, DTBB (2.5 %), THF, rt; (ii) E^+ = H_2O, Bu^tCHO, PhCHO, furfural, Me_2CO, $[Me(CH_2)_4]_2CO$, $(CH_2)_4CO$, $(CH_2)_5CO$, (–)-menthone, Ph_2CO, –78 °C; (iii) H_2O, –78 °C to rt.

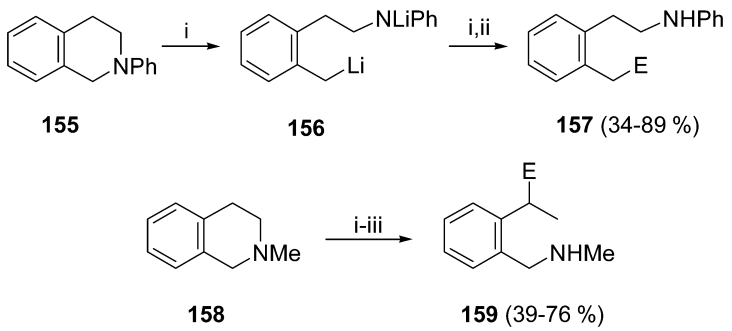
In the case of 4*H*-chromene (**150**), the DTBB-catalyzed lithiation in THF at temperatures ranging between 0 °C and room temperature is not so interesting from a synthetic point of view, because a mixture of intermediates **151** and **152** is obtained, so after quenching with water, a 2:1 mixture of the corresponding products **153** and **154** was isolated and easily separated by acid-base treatment (Scheme 29) [42].



Scheme 29 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, 0 °C to rt; (ii) H_2O.

Nitrogen-containing heterocycles

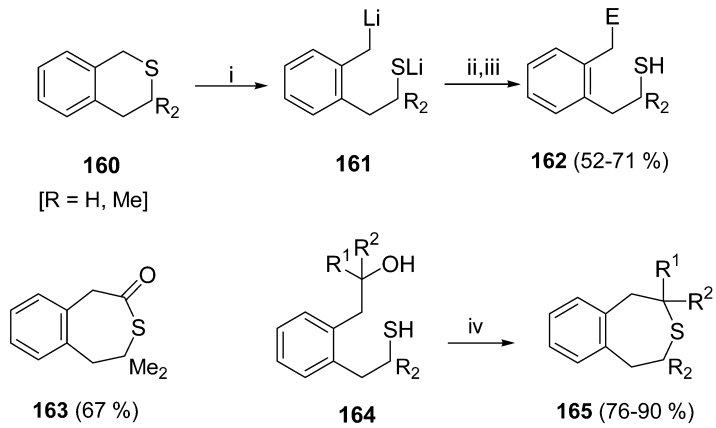
N-Phenyltetrahydroisoquinoline (**155**) was lithiated in the presence of a catalytic amount of DTBB in THF at room temperature, so intermediate **156** was prepared and after reaction with different electrophiles and final hydrolysis with water, functionalized amines **157** were the reaction products obtained (Scheme 30) [39]. For *N*-methyltetrahydroisoquinoline (**158**), and under the same reaction conditions, a surprising result was obtained; instead of the expected intermediate of type **156**, compounds **159** were isolated. An explanation for that behavior, involving a benzylic deprotonation followed by a β-elimination is given [39].



Scheme 30 *Reagents and conditions*: (i) Li, DTBB (4.5 %), THF, rt; (ii) E^+ = H_2O, D_2O, Bu^{t}CHO, PhCHO, Me_2CO, Pr^{n}CHO, $(CH_2)_4CO$, CO_2, –78 °C; (iii) H_2O, –78 °C to rt.

Sulfur-containing heterocycles

Thioisochromans (**160**) were submitted to a DTBB-catalyzed lithiation in THF at –78 °C, giving intermediates **161**. The further treatment of these compounds with different electrophiles gave, after hydrolysis with water, the expected compounds **162** (Scheme 31) [40]. With carbon dioxide, the lactone **163** was directly isolated, and hydroxy thiols **164** (resulting from the reaction of intermediate **161** with carbonyl compounds) were easily cyclized to the corresponding seven-membered heterocycles **165** under acidic conditions.



Scheme 31 *Reagents and conditions*: (i) Li, DTBB (8 %), THF, –78 °C; (ii) E^+ = D_2O, Bu^{t}CHO, Me_2CO, $(CH_2)_4CO$, CO_2, –78 °C; (iii) H_2O, –78 °C to rt; (iv) 85 % H_3PO_4, PhMe reflux.

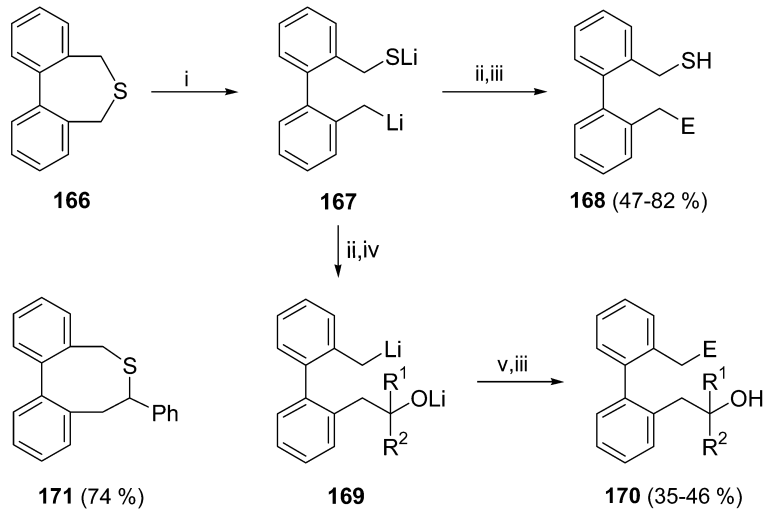
OTHER HETEROCYCLES

In this section, thiepins as well as heterocycles containing two heteroatoms, such as 1,3-dioxolanes, 1,3-dioxanes, 1,3-oxathianes, phenoxathiin, phenothiazine, and thianthrene will be considered.

Thiepins

The lithiation of 2,7-dihydrobenzothiepin (**166**) with lithium and a catalytic amount of DTBB in THF at –78 °C led to the corresponding heterocyclic ring opening, giving the intermediate **167** which, after treatment with an electrophile and final hydrolysis with 3 M hydrochloric acid, gave the expected functionalized thiols **168** (Scheme 32) [43]. Interestingly, when after the reaction of intermediate **167** with

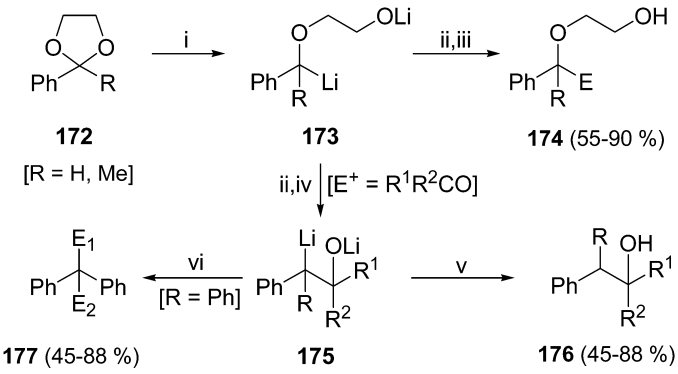
a carbonyl compound the reaction temperature was allowed to rise to room temperature, a second lithiation took place with the excess of lithium present in the reaction medium, so a second organolithium intermediate **169** was generated. After addition of a second electrophile and final hydrolysis, as mentioned above, compounds **170** were isolated. Compounds **168** derived from carbonyl compounds can be cyclized under acidic conditions, an example being the benzaldehyde derivative, which, treated with 85 % phosphoric acid under toluene reflux, gave the corresponding eight-membered heterocycle **171**.



Scheme 32 *Reagents and conditions*: (i) Li, DTBB cat. (5 mol %), THF, –78 °C; (ii) R^1R^2CO = Bu^{t}CHO, $Ph(CH_2)_2CHO$, PhCHO, Me_2CO, $[Me(CH_2)_4]_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, –78 °C; (iii) 3 M HCl, –78 °C to rt; (iv) Li, DTBB cat. (5 mol %), THF, rt; (v) E^+ = Me_2CO, Et_2CO, $(CH_2)_5CO$, $ClCO_2Et$, –78 °C.

1,3-Dioxolanes

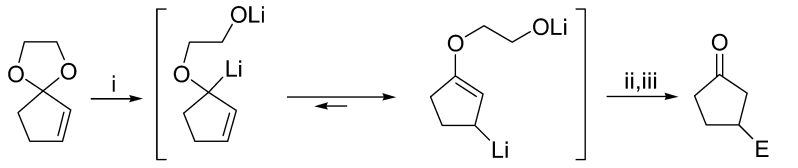
2-Phenyl-1,3-dioxolanes **172** are opened with lithium and a catalytic amount of naphthalene in THF at –40 °C to give the functionalized benzyllithiums **173**, which, by reaction with different electrophiles, afford compounds **174** (Scheme 33) [44]. When, after the reaction of intermediate **173** with a carbonyl compound, the temperature was allowed to rise to room temperature, a second carbon–oxygen cleavage



Scheme 33 *Reagents and conditions*: (i) Li, $C_{10}H_8$ (4 %), THF, –40 °C; (ii) E^+ = H_2O, D_2O, Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, –40 °C; (iii) H_2O, –40 °C to rt; (iv) –40 °C to rt; (v) H_2O or D_2O; (vi) (for $E^+ = E_1^+$ = Pr^{i}CHO, Bu^{t}CHO) E_2^+ = H_2O, D_2O, –40 °C to rt.

took place, giving a new organolithium compound **175**, able to react with a second electrophile. However, under the reaction conditions this species took a proton from the reaction medium, so a lithium–hydrogen exchange occurred and compounds **176** was isolated independently of the electrophile used. The presence of two phenyl groups at the 2-position of the starting dioxolane (R = Ph) was necessary in order to stabilize the intermediate **175** (R = Ph), so making possible the tandem introduction of two electrophilic fragments, as exemplified in compounds **177**.

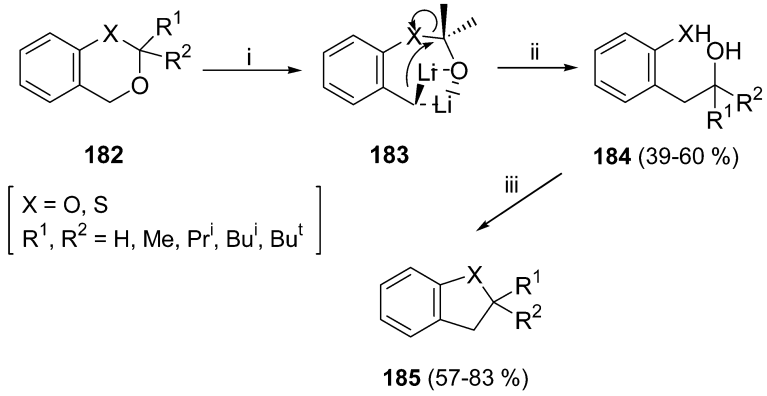
The chemistry shown in Scheme 33 was also applied to the corresponding vinylic homologs of compound **172**. Thus, using the same protocol, dioxolane **178** was opened with lithium and DTBB as the electron carrier catalyst in THF at 0 °C to yield the intermediate **179**. This species equilibrates to the most stable noncarbenoid organolithium compound **180**, which is finally trapped by the electrophile giving, after hydrolysis with water, the corresponding compounds **181** (Scheme 34) [45]. The process has synthetic interest because it represents the umpolung version of the normal reactivity of cyclopentenone, which reacts with nucleophiles at the β-position.



Scheme 34 *Reagents and conditions*: (i) Li, DTBB (2.5 %), THF, 0 °C; (ii) E^+ = Bu^{t}CHO, Me_2CO, Et_2CO, Pr$^i{}_2$CO, $(CH_2)_5CO$, 0 °C to rt; (iii) H_2O.

1,3-Dioxanes and 1,3-oxathianes

The reaction of 1,3-dioxanes and 1,3-oxathianes **182** (easily obtained from the corresponding *ortho*-substituted benzylic alcohols and carbonyl compounds) with lithium and a catalytic amount of DTBB in THF at room temperature (X = O) or –78 °C (X = S) gave an intermediate of type **183**, which suffered intramolecular nucleophilic substitution to yield compounds **184** (Scheme 35) [46]. Cyclization of these hydroxy phenols or thiophenols under acidic conditions gave benzofused heterocycles **185**.

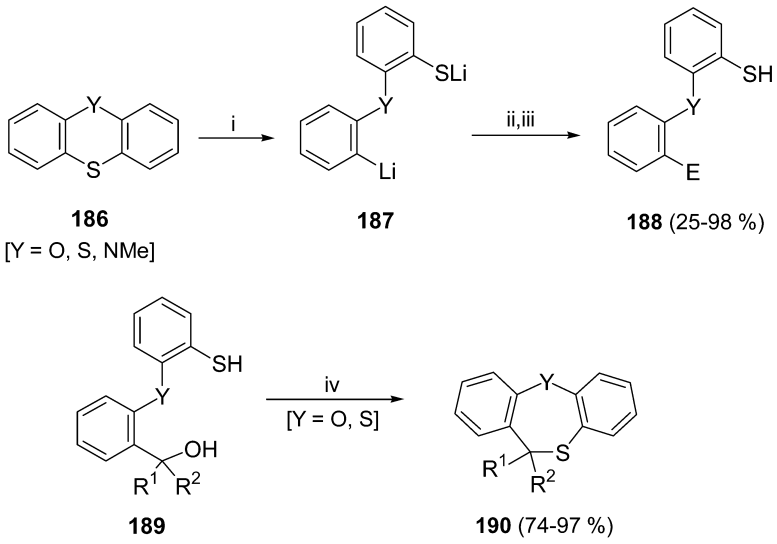


Scheme 35 *Reagents and conditions*: (i) Li, DTBB (4.5 %), THF, rt (X = O) or –78 °C (X = S); (ii) H_2O; (iii) 85 % H_3PO_4, PhMe reflux.

Phenoxathiin, phenothiazine, and thianthrene

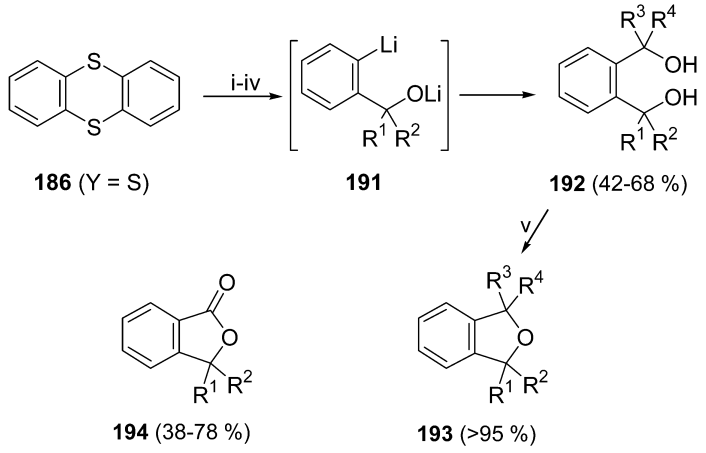
The three two-heteroatom-containing heterocycles phenoxathiin, phenothiazine, and thianthrene (**186**) were lithiated using DTBB as the catalyst in THF at –78 (Y = O, NMe) or –90 °C (Y = S), so interme-

diates **187** were obtained by a carbon–sulfur reductive cleavage. These species reacted with electrophiles giving, after hydrolysis with 3 M hydrochloric acid, the corresponding compounds **188** (Scheme 36) [47]. In the case of the oxygen- or sulfur-containing systems (Y = O, S), products **189** resulting from the reaction of intermediates **187** with carbonyl compounds were cyclized with 85 % phosphoric acid to yield the corresponding two-heteroatom-containing seven-membered heterocycles **190**.



Scheme 36 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –78 (Y = O, NMe) or –90 °C (Y = S); (ii) E^+ = H_2O, D_2O, Bu^{t}CHO, PhCHO, Ph$(CH_2)_2$CHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, –78 °C; (iii) 3 M HCl, –78 °C to rt; (iv) 85 % H_3PO_4, PhMe reflux.

Finally, when thianthrene (**186**, Y = S) was submitted to the same protocol as shown in Scheme 36, but after reacting with a first carbonyl compound (R^1R^2CO), the lithiation was continued at –90 to –78 °C in the presence of a second carbonyl compound (R^3R^4CO), a second carbon–sulfur cleavage took place, giving a new organolithium intermediate **191**, which reacted with the electrophile present in the reaction medium to afford diols **192** (Scheme 37) [47b,48]. Cyclization of these diols with 85 %



Scheme 37 *Reagents and conditions*: (i) Li, DTBB (5 %), THF, –90 °C; (ii) R^1R^2CO = PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, –90 °C; (iii) E^+ = Bu^{t}CHO, Ph$(CH_2)_2$CHO, Me_2CO, Et_2CO, CO_2, –90 to –78 °C; (iv) H_2O, –78 °C to rt; (v) 85 % H_3PO_4, PhMe reflux.

phosphoric acid under toluene reflux gave substituted phthalans **193**. When carbon dioxide was used as the second electrophile in the reaction, the process shown in Scheme 37 gave directly lactones **194**.

ACKNOWLEDGMENTS

I thank our current Ministerio de Ciencia y Tecnología and Ministerio de Educación y Deporte for continous finantial support.

REFERENCES AND NOTES

1. (a) E. J. Corey and X.-M. Cheng. *The Logic of Chemical Synthesis*, Wiley, New York (1989); (b) K. C. Nicolaou and E. J. Sorensen. *Classic in Total Synthesis*, VCH, Weinheim (1996).
2. See, for instance, "Aims and Scope". In *Adv. Synth. Catal.* **343**, A3 (2001): "While total synthesis reached extraordinary levels of sophistication in the last century, the development of practical and efficient synthetic methodologies is still in its infancy" (R. Noyori, Ed.).
3. A. Boudier, L. O. Bromm, L. Lotz, P. Knochel. *Angew. Chem., Int. Ed.* **39**, 4414 (2000).
4. For some monographs on organolithium chemistry, see: (a) B. J. Wakefield. *Organolithium Methods*, Academic Press, London (1988); (b) *Lithium Chemistry. A Theoretical and Experimental Overview*, A.-M. Sapse and P. von Ragué Schleyer (Eds.), Wiley, Chichester (1995); (c) J. Clayden. *Organolithiums: Selectivity for Synthesis*, Pergamon Press, Oxford (2002).
5. For reviews on functionalized organolithium compounds, see: (a) C. Nájera and M. Yus. *Trends Org. Chem.* **2**, 155 (1991); (b) C. Nájera and M. Yus. *Recent Res. Devel. Org. Chem.* **1**, 67 (1997); (c) M. Yus and F. Foubelo. *Rev. Heteroatom Chem.* **17**, 73 (1997); (d) C. Nájera and M. Yus. *Curr. Org. Chem.* **7**, 867 (2003).
6. First account from our laboratory: M. Yus and D. J. Ramón. *J. Chem. Soc., Chem. Commun.* 398 (1991).
7. For reviews on arene-catalyzed reactions, see: (a) M. Yus. *Chem. Soc. Rev.* **25**, 155 (1996); (b) D. J. Ramón and M. Yus. *Eur. J. Org. Chem.* 225 (2000). (c) M. Yus. *Synlett* 1197 (2001); (d) M. Yus and D. J. Ramón. *Latv. J. Chem.* 79 (2002); (e) D. J. Ramón and M. Yus. *Rev. Cubana Quim.* **14**, 75 (2002); (f) M. Yus. In *The Chemistry of Organolithium Compounds*, Z. Rappoport and I. Marek (Eds.), Wiley, Chichester (2003). In press.
8. For mechanistic studies, see: (a) M. Yus, R. P. Herrera, A. Guijarro. *Tetrahedron Lett.* **42**, 3455 (2001); (b) M. Yus, R. P. Herrera, A. Guijarro. *Chem. Eur. J.* **8**, 2574 (2002); (c) R. P. Herrera, A. Guijarro, M. Yus. *Tetrahedron Lett.* **44**, 1309 (2003); (d) R. P. Herrera, A. Guijarro, M. Yus. *Tetrahedron Lett.* **44**, 1313 (2003).
9. For a polymer-supported, arene-catalyzed version of this reaction, see: (a) C. Gómez, S. Ruiz, M. Yus. *Tetrahedron Lett.* **39**, 1397 (1998); (b) C. Gómez, S. Ruiz, M. Yus. *Tetrahedron* **55**, 7017 (1999); (c) M. Yus, C. Gómez, P. Candela. *Tetrahedron* **58**, 6207 (2002); (d) T. Arnauld, A. G. M. Barrett, B. T. Hopkins. *Tetrahedron Lett.* **43**, 1081 (2002).
10. For a review, see: D. Guijarro and M. Yus. *Recent Res. Devel. Org. Chem.* **2**, 713 (1998).
11. For a review, see: F. Foubelo and M. Yus. *Trends Org. Chem.* **7**, 1 (1998).
12. A. Guijarro, C. Gómez, M. Yus. *Trends Org. Chem.* **8**, 65 (2000).
13. F. Alonso, P. Candela, C. Gómez, M. Yus. *Adv. Synth. Catal.* **345**, 275 (2003), and references cited therein.
14. F. Alonso, C. Vitale, G. Radivoy, M. Yus. *Synthesis* 443 (2003).
15. D. Seebach. *Angew. Chem., Int. Ed. Engl.* **18**, 239 (1979).
16. (a) A. Bachki, F. Foubelo, M. Yus. *Tetrahedron: Asymmetry* **6**, 1907 (1995); (b) A. Bachki, F. Foubelo, M. Yus. *Tetrahedron: Asymmetry* **6**, 2997 (1996).
17. See, for instance: K. Sato, K. Suzuki, M. Ueda, M. Katayama, Y. Kajihara. *Chem. Lett.* 1469 (1991).

18. (a) T. Soler, A. Bachki, L. R. Falvello, F. Foubelo, M. Yus. *Tetrahedron: Asymmetry* **9**, 3939 (1998); (b) T. Soler, A. Bachki, L. R. Falvello, F. Foubelo, M. Yus. *Tetrahedron: Asymmetry* **11**, 493 (2000).
19. (a) L. R. Falvello, F. Foubelo, T. Soler, M. Yus. *Tetrahedron: Asymmetry* **11**, 2063 (2000); (b) M. Yus, T. Soler, F. Foubelo. *Tetrahedron: Asymmetry* **12**, 801 (2001).
20. (a) J. Almena, F. Foubelo, M. Yus. *Tetrahedron Lett.* **34**, 1649 (1993); (b) J. Almena, F. Foubelo, M. Yus. *J. Org. Chem.* **59**, 3210 (1994).
21. P. Beak and A. I. Meyers. *Acc. Chem. Res.* **19**, 356 (1986).
22. R. W. Hoffmann, T. Rühe, F. Chemla, T. Zahneisen. *Liebigs Ann. Chem.* 719 (1992).
23. For a review, see: F. Alonso and M. Yus. *Recent Res. Devel. Org. Chem.* **1**, 397 (1997).
24. J. Almena. Ph.D. dissertation, Universidad de Alicante (1996).
25. A. Bachki, L. R. Falvello, F. Foubelo, M. Yus. *Tetrahedron: Asymmetry* **8**, 2633 (1997).
26. J. Almena, F. Foubelo, M. Yus. *Tetrahedron* **50**, 5775 (1994).
27. See, for instance: R. B. Bates, L. M. Kroposky, D. E. Potter. *J. Org. Chem.* **48**, 609 (1972).
28. J. Almena, F. Foubelo, M. Yus. *Tetrahedron* **53**, 5563 (1997).
29. D. J. Ramón and M. Yus. *Tetrahedron* **48**, 3585 (1992).
30. J. Almena, F. Foubelo, M. Yus. *Tetrahedron* **51**, 3351 (1995).
31. M. Yus, T. Soler, F. Foubelo. *Tetrahedron* **58**, 7009 (2002).
32. F. Foubelo, C. Gómez, A. Gutierrez, M. Yus. *J. Heterocycl. Chem.* **37**, 1061 (2000).
33. (a) I. M. Pastor and M. Yus. *Tetrahedron Lett.* **41**, 1589 (2000); (b) I. M. Pastor and M. Yus. *Tetrahedron* **57**, 2371 (2001).
34. J. Gomis, I. M. Pastor, M. Yus. *Tetrahedron* **57**, 5799 (2001).
35. M. Yus and J. Gomis. *Eur. J. Org. Chem.* 1989 (2002).
36. M. Yus and J. Gomis. *Eur. J. Org. Chem.* 2043 (2003).
37. (a) A. Bachki, F. Foubelo, M. Yus. *Tetrahedron Lett.* **39**, 7759 (1998); (b) M. Yus, F. Foubelo, J. V. Ferrández, A. Bachki. *Tetrahedron* **58**, 4907 (2002).
38. M. Yus, F. Foubelo, J. V. Ferrández. *Eur. J. Org. Chem.* 2809 (2001).
39. J. Almena, F. Foubelo, M. Yus. *Tetrahedron* **52**, 8545 (1996).
40. J. Almena, F. Foubelo, M. Yus. *J. Org. Chem.* **61**, 1859 (1996).
41. J. Almena, F. Foubelo, M. Yus. *Tetrahedron* **51**, 3365 (1995).
42. M. Yus, F. Foubelo, J. V. Ferrández, A. Bachki. *Tetrahedron* **58**, 4907 (2002).
43. M. Yus and F. Foubelo. *Tetrahedron Lett.* **42**, 2469 (2001).
44. J. F. Gil, D. J. Ramón, M. Yus. *Tetrahedron* **49**, 9535 (1993).
45. J. F. Gil, D. J. Ramón, M. Yus. *Tetrahedron* **50**, 3437 (1994).
46. P. K. Choudhury, J. Almena, F. Foubelo, M. Yus. *Tetrahedron* **53**, 17373 (1997).
47. (a) M. Yus, F. Foubelo, J. V. Ferrández. *Chem. Lett.* 726 (2002); (b) M. Yus, F. Foubelo, J. V. Ferrández. *Tetrahedron* **59**, 2083 (2003).
48. M. Yus, F. Foubelo, J. V. Ferrández. *Tetrahedron Lett.* **43**, 7205 (2002).