

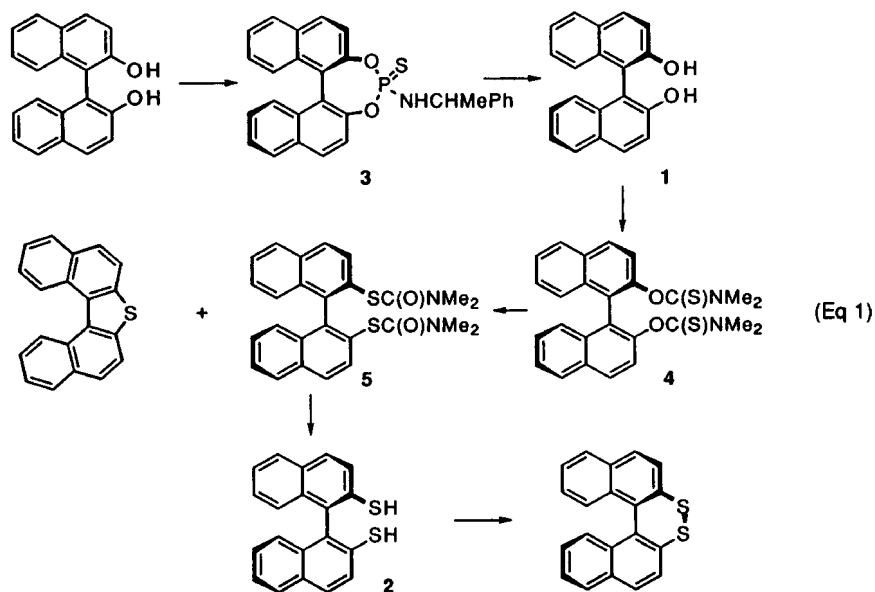
High symmetry chiral auxiliaries containing heteroatoms

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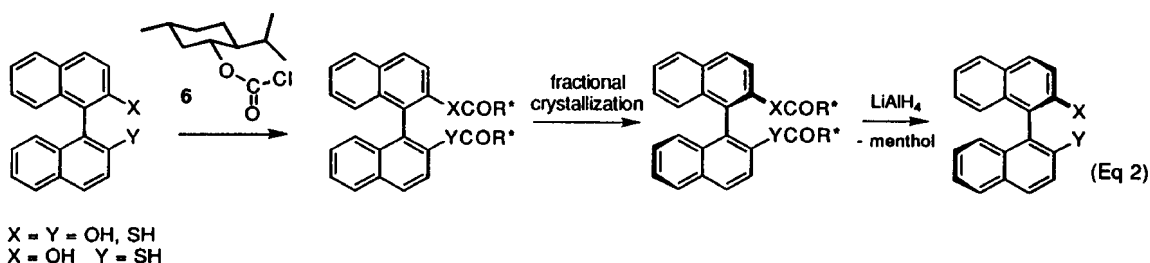
Abstract: Based on 1,1'-binaphthalene-2,2'-diol **1**, that is considered the prototype of the class of "man-made" chiral auxiliaries possessing C_2 symmetry, a variety of other chiral molecules containing the binaphthyl or biphenyl skeleton has been developed. Among them, 1,1'-binaphthalene-2,2'-dithiol **2** is the one that has experienced the largest assortment of applications.

"Man made" chiral auxiliaries are becoming increasingly popular over the classic auxiliaries directly derived from the natural chiral pool. Especially popular are those based on the binaphthyl skeleton (**1**) not only because of the high degree of optical induction that they provide, but also because these molecules incorporate a number of features that "natural" chiral auxiliaries rarely possess. For example, the high-symmetry chirality (C_2 -symmetry), the direct attachment of the functional groups to an aromatic system, the high crystallinity, the simple spectra, the possibility to access both enantiomers and the versatility to attach almost any functional group make them suitable for any occasion. Well known representative examples of this class of molecules are 1,1'-binaphthalene-2,2'-diol **1** (**2**) and the dithiol **2** (**3**).

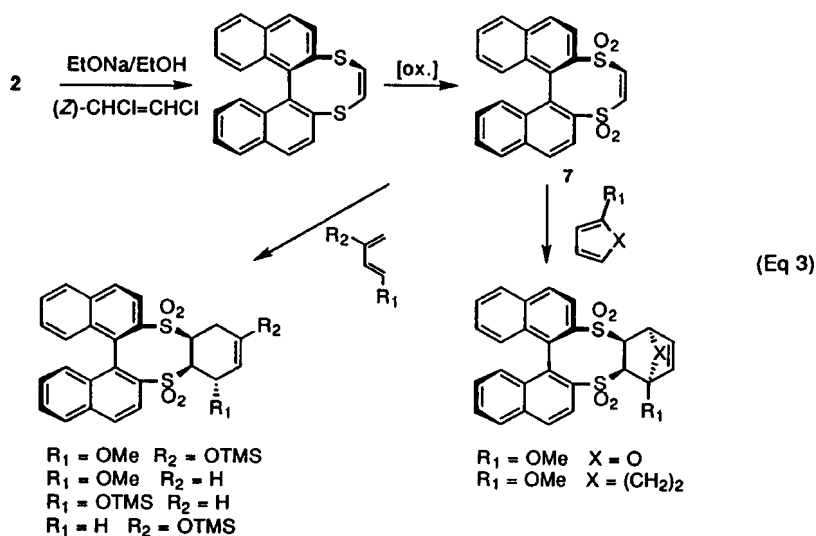


An early problem that needs to be faced when dealing with these molecules, is their preparation in enantiomerically pure form. Although in former times this fact was a serious limitation to the use of these molecules, nowadays the advancements in asymmetric synthesis and in resolution techniques (including chromatographic separation) make it possible to resolve almost any chiral molecule and thus, there is no limitation in planning chiral auxiliaries except for human imagination. Indeed, once a man-made chiral auxiliary has proved useful, the methods of resolutions may abound. For example, among the several methods that have been put forward for **1**, we have devised a resolution that makes use of thiophosphoryl chloride and (*S*)-(-)- α -methylbenzylamine (**3**). When condensed in pyridine, the two reagents afford the corresponding phosphoramidate that, reacted with racemic **1**, gives quantitatively a 1:1 mixture of diastereoisomers **3** that were cleanly separated by recrystallization in very high yield. The preparation of enantiopure dithiol **2** from enantiopure diol **1** is carried out using controlled reaction conditions in the thermolysis of the Newman-Kwart rearrangement of **4** into **5** (**4**).

More recently, we put forth a new general method of resolution applicable to many binaphthyl-substituted derivatives (5). It is based on the facile separation of the pair of diastereoisomers derived from the reaction of binaphthyl compounds with two moles of (-)-menthylchloroformate (6). (-)-(1*R*)-Menthylchloroformate is commercially available and the reaction is rapidly accomplished in toluene in the presence of triethylamine. The high difference in crystallinity between the stereoisomers allows for the obtention of the pure diastereoisomers in a single operation. The final deprotection of the hydroxy or thiol groups can be performed with LiAlH_4 , but other hydrolytic systems are probably effective as well (6).

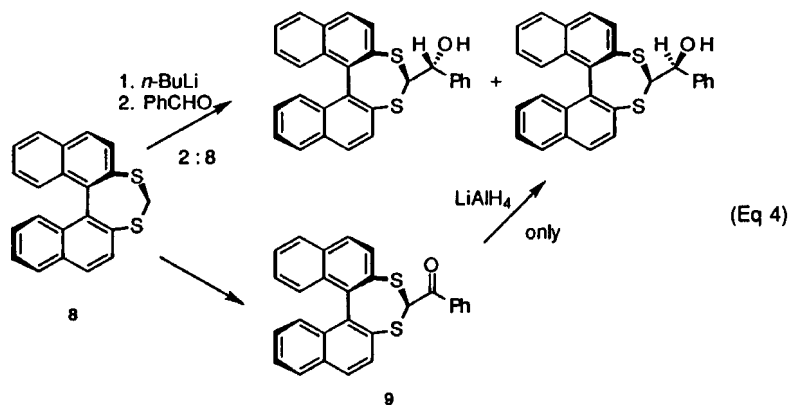


An early application of dithiol 2 as chiral acetylene equivalent is reported in Eq 3.

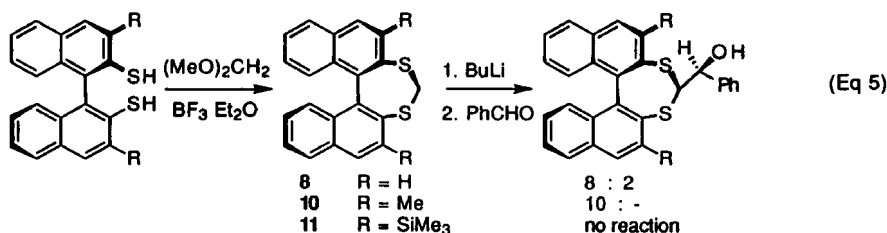


The reaction of 7 with non symmetric dienes occurs at room temperature in CH_2Cl_2 and it is in most cases completely diastereoselective affording high yields of crystalline compounds (7). Removal of the binaphthylsulfonyl group enables the synthesis of chiral molecules which would be difficult to obtain otherwise.

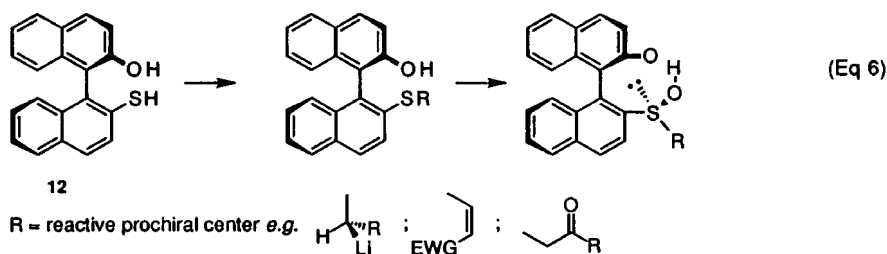
The dinaphthodithiepine 8 (Eq 4) is a C_2 -symmetric chiral variant of the dithioacetal class of reagents. The direct alkylation of its lithium salt with benzaldehyde affords an 8 : 2 mixture of diastereoisomers (8) but one single diastereoisomer is obtained by reduction of the readily available ketone 9 shown in Eq 4 (9). Other applications of 2 as chiral auxiliary have been proposed (10).



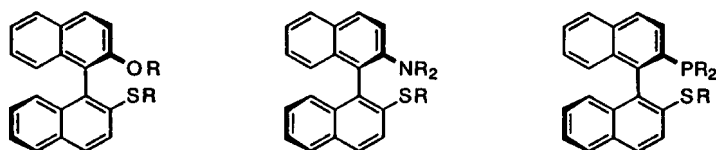
The 8 : 2 diastereoselectivity can also be upgraded to totality on adding substituents at the 3,3' positions of the binaphthyl residue as in **10** and **11** (11). The bulkyness of the groups cannot be too large as a lack of reactivity was observed for the bistrimethylsilyl substituents (Eq 5).



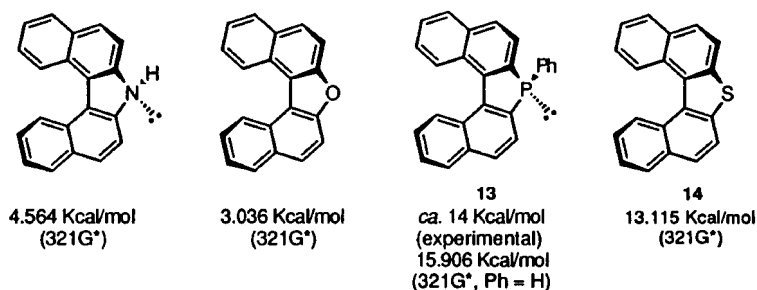
The 2'-mercapto-1,1'-binaphthalene-2-ol (**12**) (12) belongs to the class of the hydroxythiols, a class of chiral auxiliaries that has been put into profit in a number of cases (Eq 6) (13). Hydroxythiols have also been shown to be effective ligands for catalysts (14).



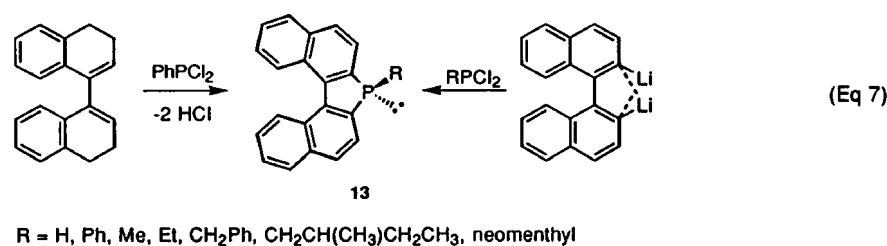
Beside the sulfur-oxygen substituents, other sulfur-heteroatom binaphthyls have been prepared with the aim of testing them as ligands for catalysts. A few examples are shown below (15).



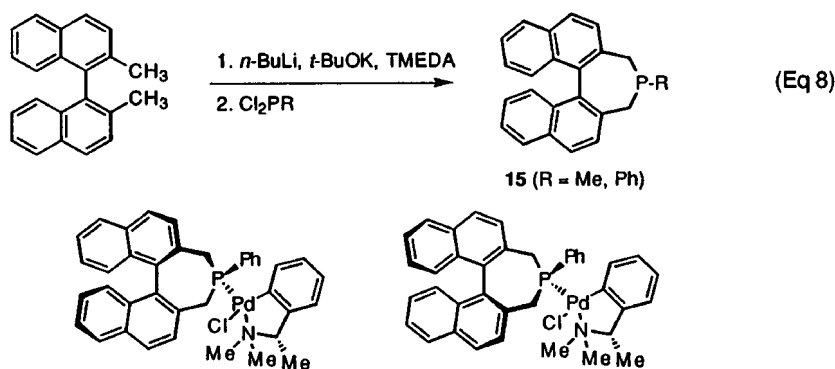
In the field of the dinaphtho-substituted five-membered ring heterocycles, we have prepared a series of representative compounds and studied their fluxional behaviour (16). While experimentally the only so far acquired result concerns the phenylphosphole **13** (17), a set of theoretical values has been obtained at the 321G* computational level for the other members (18). It is also worth mentioning that it is possible to generate the dithiol **2** from the thiophene **14** as an alternative method of this reagent (19).



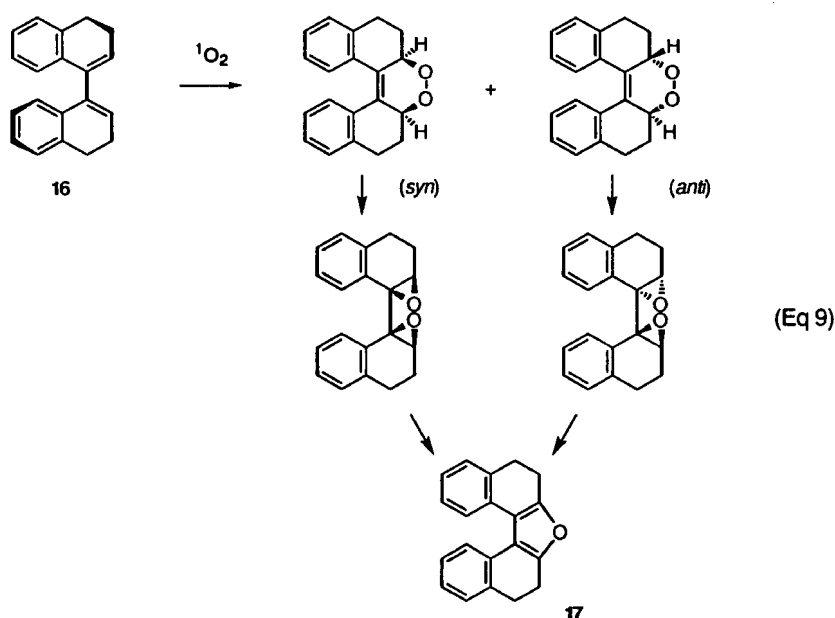
It should be noted that binaphthylphospholes are a new class of phosphorus molecules and that the parent compound exhibits an unexpected stability as compared with other unsubstituted phospholes (17). They have been prepared as shown in Eq 7.



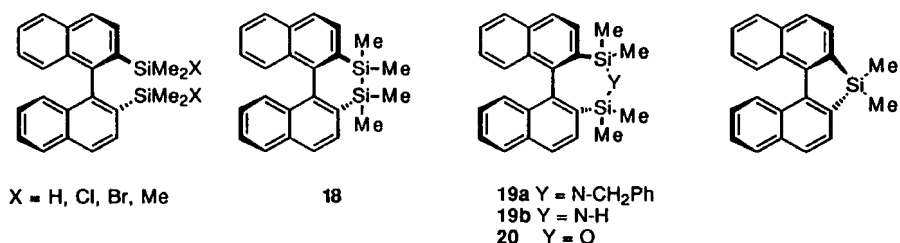
Because the labile atropisomeric nature of dinaphthophosphole **13** limits its use as chiral ligand in catalysis, the more stable dinaphthophosphepine **15** has been prepared and its antipods resolved by the diastereomeric complexes shown (Eq 8) (20). As expected the two enantiomers show no racemization at or above room temperature and thus **15** can be used for the cited aim.



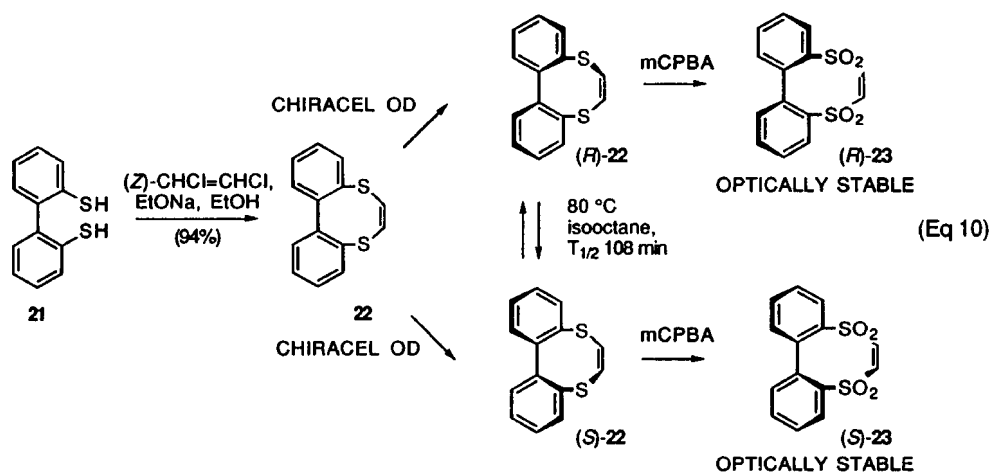
During this investigation, it was shown that the phenyl substituted phosphole **13** could be obtained by cycloaddition of dichlorophenylphosphine to bisdialine **16**. Bisdialine proved also to be a peculiar diene with other dienophiles due to its inability to lay planar. As an example, cycloaddition of singlet oxygen gives both the *syn* and the *anti* isomers (Eq 9) (21). On heating, the two endoperoxides can be transformed into the bis-epoxides shown which in turn dehydrate to the furane **17**.



Silicon-substituted binaphthyl derivatives have also been prepared starting from 2,2'-dilithio-1,1'-binaphthalene and *sym*-dichlorotetramethyldisilane [(Me₂SiCl)₂] (**22**). The disilane **18** was the starting material for most of the other binaphthyl derivatives of silicon shown. The aim was to use them as chiral STABASEs but the facile hydrolysis of the silazanes **19a,b** to the siloxane **20** has so far limited their use.



The lower atropisomerisation energy of the biphenyl in respect to the binaphthyl group can be put into profit in some case. For example, starting from the dithiol **21** (**23**) the fluxional dithiocine **22** can be obtained that was separated at room temperature into both enantiomers (Eq 10). Since the two atropoisomers (*R*)- and (*S*)-**22** interconvert at 80 °C, in principle, it is possible to effect a total resolution, *i.e.* to obtain a single enantiomer starting from the racemic mixture (**24**). Furthermore, since the oxidized form **23** is optically stable, the final reagents can be store indefinitely without loss of enantiomeric purity.



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