Synthesis and stereoselective functionalization of silylated heterocycles as a new class of formyl anion equivalents

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The fluoride ion-induced reactivity of a series of silyl heterocycles leads to the generation of nucleophilic species capable of interacting with electrophiles, thus disclosing new classes of formyl and acyl anion synthons. Moreover, when reacting stereodefined molecules, the stereoinformation of the reacting carbon–silicon bond is transferred to the newly formed carbon–carbon bond, suggesting possible applications in stereoselective synthesis. Thus, silyl dithiolanes, oxathiolanes, dioxolanes, thiazolidines and oxazolidines can be efficiently and stereoselectively functionalized under fluoride ion conditions in the presence of electrophiles. While direct access to silyl heterocycles is generally either prevented or troublesome, a novel protocol for their synthesis has also been developed, together with a simple general access route to several functionalized and stereodefined mercaptans, building blocks for the construction of silyl heterocycles.

Introduction

Umpolung reactivity is a valuable synthetic strategy in organic synthesis, providing unconventional access to molecules through the formation of bonds *via* the inversion of normal reactivity.[1]

In this context, the development of synthetic equivalents to acyl anions has recently attracted a great deal of interest for the synthetic potential that such reactions may disclose. In relation to this, suitably protected carbonyl derivatives represent a very interesting class of compounds that are able to act as equivalents to acyl anions, and there are now a wide range of molecules that can behave in this way.

Several acyclic derivatives have been shown to react as masked formyl and acyl anion synthons. Some selected examples are α-silyl sulfides ($PhSCH_2TMS$[2] and MeO(PhS)CHTMS[3]), α-lithiated derivatives such as tris(phenylthio)methyllithium[4] and methoxy(phenyldimethylsilyl)methyllithium,[5] and α-metalated enol carbamates.[6] Formaldehyde hydrazones have been used as neutral formyl anion equivalents in Michael additions to conjugated enones,[7] while protected hydroxymalonitriles were reported for the preparation of activated esters in the synthesis of dipeptides.[8]

Thioacetals are probably one of the most versatile classes of acyl anion equivalents, and among them, heterocyclic examples offer a variety of methods for the development of such reactivity. For a long time, two of the most commonly used

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classes of cyclic *S*,*S*-acetals have been 1,3-dithianes and 1,3-dithiolanes, which are useful carbonyl protecting groups and can react as masked acyl carbanions.[9] These compounds are easier to obtain with respect to their oxygen analogues and more stable to hydrolytic cleavage due to their stability towards acidic and basic conditions. Many methods for their unmasking are reported, but several require harsh conditions, frequently use heavy and toxic metal ions, have long reaction times, suffer for the occurrence of side reactions and often lack generality.[10]

1,3-Dithianes can be easily metalated with BuLi and reacted with a wide range of electrophiles, thus demonstrating their behaviour as useful synthons and umpoled reagents.[9,11] On the other hand, deprotonation of related 1,3-dithiolanes invariably leads to unstable anions and cleavage of the heterocyclic ring is always reported, thus limiting their use in functionalization under strong basic conditions.[12]

Despite the large scale application of these cyclic *S*,*S*-acetals, the use of chiral 1,3-dithianes did not afford any success in stereoselective synthesis, and thus different heterocycles have been considered, such as 1,3-oxathianes,[13] 1,3-dioxanes[14] and 1,4-oxazines as representative examples.[15] Also, mono- and disulfoxides of dithianes have found increasing applications in asymmetric synthesis in recent years.[16]

Besides six-membered heterocycles, five-membered ring heterocyclic derivatives are valuable intermediates in organic synthesis. Compounds containing either one heteroatom, as in furans and pyrrolidines, or derivatives bearing two or more heteroatoms have played an important role in different synthetic strategies. Among these latter structures, 1,3-dioxolanes,[14b,17] 1,3-oxathiolanes,[18] 1,3-thiazolidines, 1,3-oxazolidines, imidazolines and benzotriazole derivatives[19] have found large scale application as building blocks for the construction of more complex molecules.[15]

In recent years, chiral acyl anion equivalents have seen increased use in asymmetric synthesis. There are many examples of chiral masked acyl carbanions, and several reports deal with five-membered heterocyclic systems.

Lithiated chiral oxazolidinones, including compounds derived from camphor,[20] have been reported to react with aldehydes, ketones and imines, leading to enantioselective formylation of the carbonyl compounds.[21] Oxazolidines have also found applications as chiral formyl anion equivalents, either for direct metalation in the presence of (−)-sparteine[22] or through the transmetalation of tributylstannyl derivatives with BuLi and condensation with benzaldehyde.[23] Thiazolidines, upon treatment with BuLi and aldehydes or ketones in the presence of (−)-sparteine, also afforded products with high ee but moderate diastereoselectivity.[24] Isopropyl *N*-Boc-thiazolidines have been used as chiral organolithium compounds in the addition to aldehydes, leading to products in good stereoselectivity.[25] Thiazolidines are also metalated with BuLi *via* their respective formamidines, but 40–50% fragmentation of the heterocyclic ring has been observed.[26] Chiral dioxolanes[23a] and dioxolanones[17] have also found applications as acyl anion equivalents.

In recent years, the chemistry of organosilicon compounds has witnessed an unbelievable growth as a consequence of the critical role it plays in many chemical and biochemical transformations. Extensive investigations have been carried out over the years, outlining these compound's tolerance of other functional groups and their versatility as intermediates in organic synthesis.

Thus, reagents and methods based on organosilicon chemistry are an area of increasing interest in organic synthesis. The application of heterocyclic silanes to organic synthesis offers the opportunity for new synthetic strategies, since these compounds can behave as effective precursors to heterocyclic carbanions and as masked functional group equivalents. In this field the reactivity of 2-(trimethylsilyl)oxazoles and oxazolines, their stannylated analogues[27] as powerful building blocks and their synthetic utility with respect the corresponding 2-lithio derivatives have been reported, providing molecules which are unaccessible by classical metallation.

Moreover, 2-(trimethylsilyl)thiazole has been shown to be a versatile reagent, leading to carbodesilylation reactions with various electrophiles. When chiral aldehydes were used, a good diastereoselectivity was achieved in the final adducts.[28]

Silyl 1,3-dithianes

1,3-Dithianes have been widely used as acyl anion equivalents, and some examples of silyl dithiane functionalization have been reported.[9d] Nonetheless, fluoride-induced proto- or carbodesilylation of such molecules has never been applied in stereoselective synthesis.

On the other hand, it is firmly established that metalation of 1,3-dithianes[11,29] and 1,3-diselenanes[30] occurs regioselectively at C-2 at the equatorial hydrogen rather than at the axial hydrogen, and that their metallo derivatives lead invariably, upon reaction with electrophiles, to products bearing the incoming group at the equatorial position, whatever the other substituent eventually present at C-2 is. Krief and co-workers have extensively investigated the related 4,6-disubstituted six-membered rings, 1,3-dithianes and diselenanes, and found that

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their treatment, even at very low temperatures (down to −130 °C), still affords invariably the equatorially-functionalized products, irrespective of the configuration of the 2-substituted starting compound.[31]

Axial functionalization has nevertheless been obtained in the diselenane series upon reacting 4,6-dimethyl-2-methylseleno-1,3-diselenane through a Se/Li exchange. On the other hand, when the same protocol was applied to the dithiane series, again, the equatorial isomer was the sole product obtained, providing evidence in this case of an unexpectedly lower configurational stability.

Furthermore, some examples of the functionalization of a C–Si bond to a new C–C bond with retention of configuration has been reported. In fact, with the exception of allylsilanes,[32] there are only a few cases of stereoselective synthetic transformations of sp^3 C–Si bonds to C–C bonds. Such examples include conversions of the C–Si bonds of epoxysilanes to C–C bonds upon reaction with aldehydes,[33] stereoselective insertion into strained bonds,[34] palladium-catalyzed conversions of chiral trifluoro benzyl silanes to chiral diaryl silanes,[35] the diastereoselective intramolecular reaction of a benzyl silane,[36] retention of configuration in the desilylative hydroxymethylation of α-silyl sulfides[37] and, more recently, the reactivity of chiral benzyl silanes[38] and silylated aziridines[39] with aldehydes.

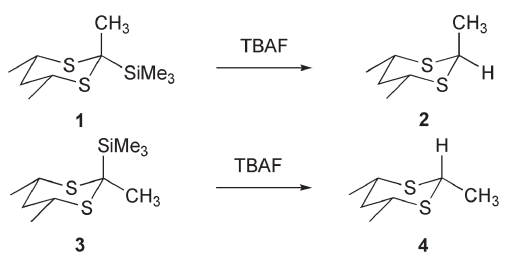
A recent investigation on the fluoride ion-induced protodesilylation of sterically defined silyl dithianes, has, on the other hand, uncovered a novel interesting example of protodesilylation with retention of configuration.[40]

Thus, for instance, both *cis*- (**1**) and *trans*- (**3**) 2-silyl-2,4,6-trimethyl dithiane, when subjected to fluoride-induced desilylation with TBAF at rt for 4 h, reacted smoothly to afford the corresponding 1,3,5-trimethyl dithianes **2** and **4**, respectively, in good yields with clean retention of configuration (Scheme 1).

The possible effect of carbanion-stabilizing species on C-2 in the stereochemistry of the desilylation was also considered, and it was shown that even in the presence of a further sulfurated moiety (Table 1, entries 1 and 2) or a sulfoxide group (Table 1, entries 3 and 4), no trace of epimerization could be detected, thus showing an interesting generality of this behaviour.

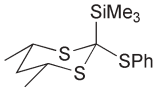
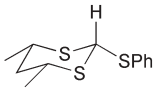
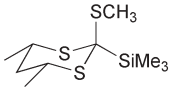
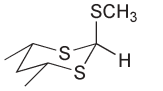
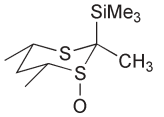
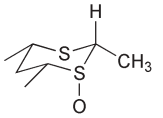
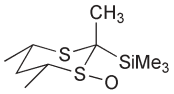
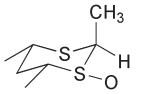
2,2-Bis-trimethylsilyl-1,3-dithiane was also investigated in order to ascertain whether there could be a possible discrimination between the two identical silyl groups, and it was found that the trimethylsilyl moiety in the equatorial position is the more reactive.

When 2-trimethylsilyl-2-phenyl-4,6-dimethyl-1,3-dithiane **5** was taken into consideration, the result of the desilylation



Scheme 1

Table 1 Desilylation of substituted silyl dithianes

Entry	Substrate	Product	Yield (%)
1			100
2			98
3			98
4			90

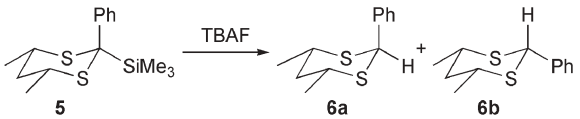
reaction was less straightforward, appearing to be a function of temperature and the equivalents of TBAF used (Scheme 2). Low temperatures (−5 °C) and a catalytic amount of TBAF lead to a low yield of **6a**, while at higher temperatures (25 °C) only **6b** was isolated. Intermediate temperatures afforded mixtures of **6a** and **6b**. Such behaviour was rationalized through a still stereoconservative desilylation, but due to the increased acidity of the C-2 hydrogen α to the aromatic ring, epimerization of **6a** into **6b** followed.

These results therefore most likely indicate that all the reported reactions proceed through a pentacoordinated silicon intermediate rather than through a free carbanion, which should be expected to epimerize easily.

Thus, once established that protodesilylation occurs with retention of configuration, the more synthetically useful carbodesilylation reactions were examined with the aim of checking whether such stereoconservative behaviour could be extended to the formation of new C–C bonds. Thus, various stereochemically defined silyl dithianes, **7**, **9** and **11**, were reacted with electrophiles and showed interesting stereoconservative functionalization (Table 2).

All the reactions yielded the corresponding adducts in good yield. While the reactions of **7** appear quite obvious (Table 2, entries 1–6), and disclose an alternative and milder methodology for functionalizing such molecules, the reactions of the *trans* diastereoisomer **9** yielded products **10** (Table 2, entries 7–11), in which the electrophile is unequivocally in the axial position.

Such results outlined for the first time a successful, selective functionalization of the axial position of such molecules, suggesting interesting applications in stereoselective synthesis.

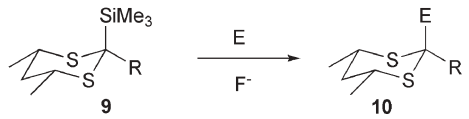


Scheme 2

Table 2 Stereoselective functionalization of silyl dithianes

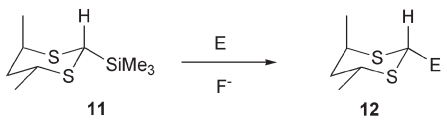
7 **8**

Entry	R	E	Yield (%)
1	H	CH_3I	31
2	H	Ph–CHO	72
3	H	C_6H_{11}–CHO	56
4	H	2-Furyl–CHO	76
5	H	(*p*-CH_3O)–C_6H_4–CHO	74
6	$SiMe_3$	CH_3I	59



9 **10**

Entry	R	E	Yield (%)
7	H	CH_3I	26
8	H	Ph–CHO	63
9	H	C_6H_{11}–CHO	47
10	H	2-Furyl–CHO	70
11	H	(*p*-CH_3O)–C_6H_4–CHO	56



11 **12**

Entry	R	E	Yield (%)
12	H	C_6H_{11}–CHO	78
13	H	2-Furyl–CHO	85
14	H	(*p*-CH_3O)–C_6H_4–CHO	87

Silyl heterocycles synthesis

As mentioned above, 1,3-dithiane anions have been extensively used in the last few decades as masked acyl carbanions in umpolung reactivity and have had a substantial impact on synthetic organic chemistry.[9] Nonetheless, although several methods for their unmasking have been reported,[10] they still suffer from the generally harsh conditions required for their unprotecting. On the other hand, dioxolanes, oxathiolanes, dithiolanes and even thiazolidines have been reported to be unmasked under milder conditions, thus possibly giving a broader spectrum of applications to such molecules in the generation of formyl and acyl anion equivalents. Unfortunately, such heterocycles generally suffer difficulties in their functionalization under strongly basic conditions. For instance, 1,3-dithiolane anions, upon treatment with bases, have been reported to undergo either deprotonation at C-2, with subsequent cycloelimination to dithiocarboxylate anions and ethylene derivatives,[12c] or C-4, to afford products derived from thiocarbonyl derivatives and vinyl thiolate anion.[12a,b] A similar behaviour was observed in unsubstituted dioxolanes, whose anions undergo fragmentation. Thiazolidines are also reported to be metalated, but only in the presence of specific nitrogen protecting groups. Only two examples of dithiolanes bearing an electron withdrawing group undergoing functionalization in basic conditions are reported in the literature, thus indicating the remaining need for a general protocol for their functionalization.[41] Thus, taking advantage of the previously outlined results for the reactivity of dithianes, which seem to occur *via* pentacoordinated silicon species and not a free carbanion, we envisaged that functionalization of the C–Si bond could possibly lead to a solution to the problem, and to the development of a novel and general functionalization methodology for such labile heterocycles.

In this context, since direct access to silyl heterocycles is difficult or even prevented, an alternative route to such molecules had to be devised.

A general route to silyl dithiolanes and, more generally, five-membered ring silylated heterocycles could be envisaged through the simple reaction of bifunctional molecules, such as dithiols, amino alcohols, amino thiols and mercapto alcohols with formyl trimethylsilane. Difficulties encountered in the generating and handling of such a labile molecule[42] led to the search for a possible synthetic equivalent of such a compound, and we envisaged bromo(methoxy)methyl trimethylsilane (**14**) to be the reagent of choice. In fact, such a molecule can be obtained in a quantitative yield by the treatment of commercially available methoxymethyl trimethylsilane (**13**) with bromine and a subsequent one-pot treatment with the required mercaptan (Scheme 3).[43]

The reaction proved quite general, occurring under very mild conditions, affording usually in very good yield the corresponding heterocycles **15**. Nonetheless, a possible limitation to such a procedure could be the difficult availability of the required functionalized mercaptans.

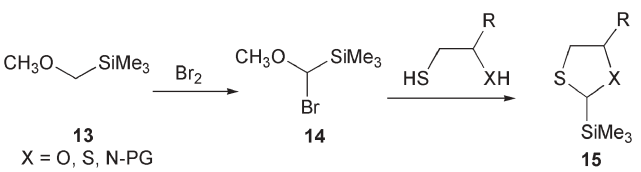
A possible general route to structures of type $HSCH_2CH_2XH$ was envisaged in the reactivity of a particular compound, $(TMS)_2S$ (HMDST), which proved recently to be a very useful intermediate in the transfer of sulfurated functionalities[44] with ring strained molecules such as oxiranes, thiiranes and aziridines.

The ring opening of epoxides with various nucleophiles is actually an important and useful synthetic transformation for easy access to a large number of functionalized intermediates, useful in the synthesis of more complex organic structures.[45]

In this context, reactions with sulfurated nucleophiles play an important role,[46] and in particular, the ring opening of oxiranes with thiols yields β-hydroxy thioethers, which represent starting compounds for the synthesis of leukotrienes[47] of HIV-1 protease inhibitors[48b] and MMP inhibitors.[48a] Such ring openings are promoted by either Lewis acids or basic catalysts, and afford α-hydroxy sulfides in good yields with a high degree of regiochemical control.

Thiosilanes have also been used as nucleophiles in reactions with oxiranes in place of thiols.[47c,49]

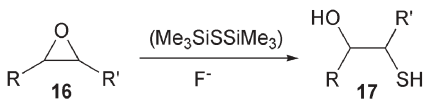
Nonetheless, among the reactions of sulfur nucleophiles with epoxides, there are a few methods which allow direct



13 X = O, S, N-PG **14** **15**

Scheme 3

Table 3 Direct synthesis of β-mercaptoalcohols



Entry	R	R′	Yield (%)
1	Me	H	65[a]
2	Ph	H	95[b]
3	$^{i}PrOCH_2$	H	72[c,d]
4	CH_2=$CHCH_2OCH_2$	H	87
5	$ClCH_2$	H	40[e]
6	CH_2=CH	H	80[f]
7	CH_3	CH_3	55
8	Cyclohexyl	Cyclohexyl	90

[a] 2-(trimethylsilyloxy)propane-l-thiol was isolated (72%) by using 10% TBAF. [b] 4.6% of the regioisomer. [c] 2.5% of the regioisomer. [d] Silyl ether was obtained with 0.3 equiv. of TBAF (90%). [e] 70% of silyl ether was obtained with 0.3 equiv. of TBAF. [f] 18% of silyl ether was recovered.

access to β-mercapto alcohols. Some procedures involve reactions of H_2S,[50] $NaBH_2S_3$[44a] and thiourea.[51]

In relation to this, it is worth mentioning the ring opening of epoxides induced by silanethiols such as Ph_3SiSH[49c] and $^{i}Pr_3SiSH$,[52] which behave as mono-protected H_2S but are easier to handle and afford the desired β-hydroxy thiols in high yields.

Thus, treatment of variously functionalized oxiranes **16** with HMDST at rt in the presence of a catalytic amount of TBAF led simply and smoothly to 2-substituted 1-mercaptoethan-2-ols **17** (Table 3), arising from a clean regioselective attack of the sulfurated nucleophile on the less hindered side of the oxirane, disclosing a potentially useful and straightforward route to 1,2-mercaptoalcohols.[53]

The reactivity proved general, leading to the synthesis of substituted 1,2-mercaptoalcohols bearing aromatic, aliphatic and vinylic moieties.[54]

Due to the mildness of the experimental conditions, this methodology can also be applied to very useful but labile compounds such as glycidol derivatives and epichloridrin (Table 3, entries 3,4 and 5), which represent important structures in different application fields.[48a,49,55]

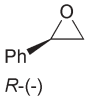
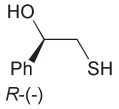
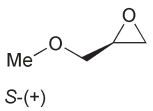
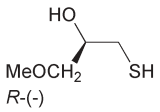
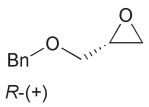
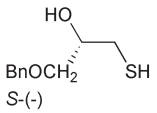
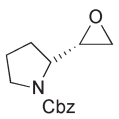
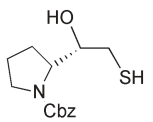
This mild and selective procedure may also be usefully applied to chiral molecules. When enantiopure epoxides were reacted under the same conditions, optically active β-hydroxy thiols were formed regioselectively (Table 4).

The reported reactivity may be conveniently extended to other ring strained compounds such as thiiranes and aziridines, affording easy access to a variety of building blocks for use in the synthesis of five-membered ring silylated heterocycles, which can be useful reagents in the synthesis of variously functionalized heterocycles.

Aziridines, in fact, due to their high propensity for acting as carbon electrophiles, are versatile intermediates for the synthesis of biologically and chemically important compounds. A number of ring opening reactions of activated and unactivated aziridines have been reported, including reactions with a wide range of heteroatom and carbon nucleophiles.[56]

The orientation of the attack generally occurs at the less sterically hindered position to provide ring opened products,

Table 4 Enantioselective synthesis of 1,2-mercaptoalcohols

Entry	Epoxide	1,2-Mercaptoalcohol	Yield (%)
1	 *R*-(-)	 *R*-(-)	95[a]
2	 *S*-(+)	 *R*-(-)	84
3	 *R*-(+)	 *S*-(-)	65
4	 *1S, 2S*-(+)	 *1S, 2S*-(+)	86[b]

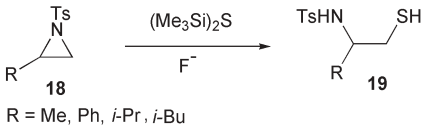
[a] 4.6% of the regioisomer was isolated. [b] Traces (3%) of silyl ether were evident.

but in some examples, the formation of mixtures of regioisomers is reported.

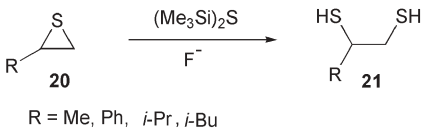
Ring opening with sulfurated nucleophiles is an interesting procedure for accessing β-amino sulfides, which are compounds of undoubted synthetic utility in organic chemistry.[57] While the nitrogens of non-activated aziridines behave as a base to form the nucleophilic thiolate anion, activated aziridines often require a strong acid (such as CF_3SO_3H)[58] or a Lewis acid (*i.e.* BF_3,[59] $ZnCl_2$[60] or $MgBr_2$,[61]). Examples of the cleavage of *N*-tosyl aziridines have been reported in water in the presence of β-cyclodextrin or PBu_3.[62] Ring opening reactions with nucleophiles can also be achieved under basic conditions (Et_3N),[63] and TBAF has been used when silylated nucleophiles have been reacted.[64] Recently, TMS–CN, TMS–N_3, TMS–Br and TMS–I were demonstrated to attack aziridines under Lewis base catalysis with a high regioselectivity.

On the other hand, probably due to their ease of polymerization and tendency to be desulfurized, ring opening reactions of thiiranes are rarely studied, even if they represent a very convenient method to introduce a sulfur heteroatom into many interesting heterocyclic systems.[65] Their ring opening reactions are generally described as taking place under Lewis acid catalysis[66] and often show poor regio- and stereoselectivity.[66a,67]

Thus, reaction of HMDST with variously functionalized aziridines **18** (Scheme 4) and thiiranes **20** (Scheme 5), in the presence of catalytic amounts of fluoride ion, led to the smooth formation of the corresponding mercaptans **19** and **21**, respectively, suitable as building blocks for accessing a variety of heterocyclic systems. Interestingly, as already observed in the case of oxiranes, the reactivity can be efficiently extended to chiral substrates so as to access stereodefined mercaptans, precursors of chiral heterocycles.[68]



Scheme 4



Scheme 5

Silyl 1,3-dithiolanes

The development of a general and reliable method to access a variety of silyl heterocycles has opened the way to a thorough investigation of their chemistry.

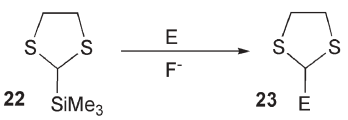
As already mentioned, simple 1,3-dithiolanes, when deprotonated at position-2, suffer from cycloreversion to the corresponding alkene and dithiocarboxylate.[12] Nonetheless, 2-ethoxycarbonyl dithiolane can be metalated, and undergoes conjugate addition to unsaturated carbonyl compounds.[69] Similarly, 1,3-benzodithiolanes have been reported to interact with different electrophiles.[70]

The racemic *trans*-disulfoxide of 1,3-dithiolanes can also be deprotonated and reacted with aldehydes with moderate to excellent diastereoselectivity.

Thus, when silyl dithiolane **22** is treated with electrophiles in the presence of different sources of fluoride ion (TBAF, TBAT, TASF), a smooth reaction occurs, leading to the corresponding functionalized α-hydroxy dithiolane **23** (together with desilylated dithiolane, *ca.* 20%), so revealing the possibility of an effective transfer of a "dithiolane anion" onto electrophiles under mild conditions (Table 5).[71] These results show that, under the present conditions, **22** can behave as a masked dithiolane anion (Fig. 1).

This reactivity may be conveniently performed with aromatic (Table 5, entries 1 and 2), heteroaromatic (Table 5, entries 3 and 4), aliphatic (Table 5, entry 6) and α,β-unsaturated aldehydes (Table 5, entry 5), affording in all cases protected α-hydroxy aldehydes. Reactive halo derivatives, such as allyl bromide (Table 5, entry 8) and methyl vinyl ketone (Table 5, entry 7), will also undergo reaction. With α,β-unsaturated aldehydes, only 1,2-adducts have been isolated, whereas reaction with methyl vinyl ketone afforded a 3 : 1 mixture of 1,2- and 1,4- adducts.

Table 5 Reactivity of silyldithiolanes



Entry	E	Yield (%)
1	Ph–CHO	79
2	(*p*-Br)–C_6H_4–CHO	78
3	2-Thienyl–CHO	83
4	*N*-Me pyrroyl–CHO	12
5	PhCH=CHCHO	81
6	$(CH_3)_2CHCH_2CHO$	80
7	CH_2=$CHCOCH_3$	30[a]
8	CH_2=$CHCH_2Br$	30

[a] 3 : 1 mixture of 1,2- : 1,4-adducts.

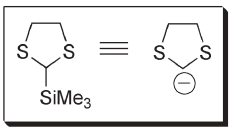


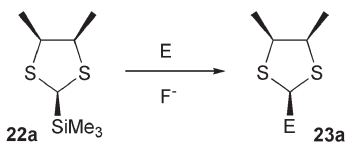
Fig. 1 Silyl dithiolane as dithiolane anion synthon.

Furthermore, the hydroxydithiolanes obtained can be easily and efficiently transformed into hydroxy aldehydes upon treatment with $Tl(NO_3)_3$, thus providing a novel synthetic route to an interesting class of compounds.

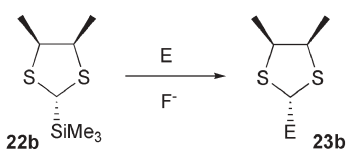
Once the possibility of an easy functionalization of silyl dithiolanes was established, the stereochemical fate of the reaction was considered.

Thus, both *cis*- and *trans*-4,5-dimethyl-2-trimethylsilyl-1,3-dithiolanes (**22a** and **22b**) were obtained from *meso*-2,3-butanedithiol with bromo(methoxy)methyl trimethylsilane (**14**) in a 1 : 3 ratio and separated by TLC. Subsequent reaction of both isomers with aldehydes, as typical electrophiles, in the presence of TBAF or CsF, led, as expected, to the corresponding adducts **23a** and **23b** in good yields (Table 6).[72] Either aromatic, heteroaromatic or aliphatic aldehydes can be efficiently reacted, and again complete retention of configuration at C-2 was maintained in both reactions. This shows that the stereoconservative behaviour observed in the dithiane series also holds also for the dithiolane series.

Table 6 Stereoselective functionalization of 4,6-disubstituted dithiolanes



Entry	E	Yield (%)
1	Ph–CHO	57
2	C_6H_{11}–CHO	38
3	2-Furyl–CHO	55
4	(*p*-CH_3O)–C_6H_4–CHO	61



Entry	E	Yield (%)
5	Ph–CHO	54
6	C_6H_{11}–CHO	33
7	2-Furyl–CHO	54
8	(*p*-CH_3O)–C_6H_4 CHO	56

Silyl 1,3-thiazolidines

The thiazolidine ring system derives special importance from the fact that it is an integral part of medicinally important compounds like penicillins[73] and some antiradiation drugs.[74] Substituted thiazolidine derivatives represent important key intermediates for the synthesis of pharmacologically active drugs.[75] Recently, a number of thiazolidines have been claimed to be retroviral protease inhibitors[75b,76] and have also been investigated as possible substitutes for the carbohydrate moiety in the synthesis of new antiviral nucleosides.[77] More recently, they have also been shown to be antitussive-active molecules.[78] Thiazolidines are also relevant in food chemistry as they are incorporated into flavor enhancing additives.[79] Their synthetic utility has been demonstrated by their use as blocking groups[80] and intermediates in the synthesis of aldehydes[81] and aminoethane thiols.[82]

Despite the utility of the thiazolidine moiety, very few methodologies for the functionalization of position-2 of the heterocyclic ring exist. In fact, to the best of our knowledge, only a few reports deal with such functionalization, and their efficiency seems to be related to the presence of specific N-protecting groups. Meyers *et al.* reported the efficient metallation of the thiazolidine ring when a *tert*-butylformamidine group was present on the nitrogen atom,[26] while, more recently, Gawley *et al.* have reported a nice functionalization of thiazolidines bearing an *N*-BOC system,[25] showing their possible use as chiral acyl anion synthons. Toru *et al.* have recently reported a very nice functionalization of *N*-Boc-protected thiazolidines in the presence of (−)-sparteine,[24] which afforded the corresponding adducts with low de values but with very interesting ee (up to 93%).

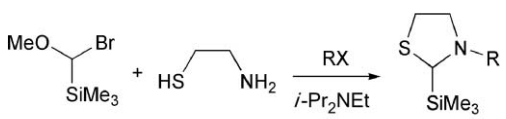
Silyl thiazolidines can be easily accessed through the previously mentioned procedure *via* the reaction of **14** *in situ* with aminoethanethiol (Table 7). The thiazolidine thus obtained can, again *in situ*, be easily protected at the nitrogen atom with different groups, such as mesyl, tosyl, acetyl, benzoyl, cinnamoyl, BOC and Cbz, to afford a general route to various N-functionalized 2-silylthiazolidines **24** through a simple one-pot procedure (Table 7).[83]

Reaction of the so-obtained silyl thiazolidines with aldehydes under fluoride catalysis uncovered an efficient methodology for their functionalization (Table 8), showing a consistency with different protecting groups on the endocyclic nitrogen, and occurring smoothly in the presence of different *N*-protecting moieties such as tosyl, mesyl, acetyl and BOC. No reaction was observed when the protecting groups were benzoyl and cinnamoyl, with only the desilylated thiazolidine being recovered from the reaction mixture in these instances.

The versatility of the present methodology is further illustrated by another example. When the protecting group itself contains an electrophilic centre, a clean cyclization occurs, leading to polycyclic compounds in good yields. Thus, when reacting *N*-(*ortho*-formyl)benzoyl-2-trimethylsilyl-thiazolidine (**24h**) with fluoride ion, the polycyclic compound **26** can be isolated in good yield, and with an interesting de (of 70%) of the isomer with the two protons in an *anti*-configuration, as evident from its X-ray crystal structure (Scheme 6). Such a reaction opens up an easy and diastereoselective route to polycyclic derivatives with possible biological activity.

Furthermore, when the protecting group is a phthalimido or succinimido derivative of a natural amino acid, silyl thiazolidines can be obtained as mixtures of enantiopure diastereoisomers **27**, which can be separated and reacted under fluoride ion conditions to afford direct access to polycyclic derivatives **28** (Scheme 7). Interestingly, only one diastereoisomer seems to be reactive in the present conditions, affording the polycyclic derivative **28** with a very good de (>90%).

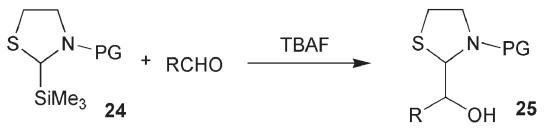
Table 7 Synthesis of N-protected silyl thiazolidines



14 **20** **24a-h**

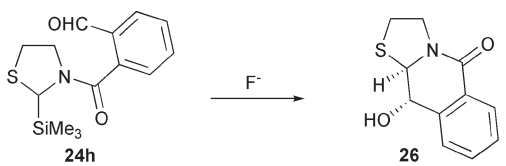
Entry	R	Product	Yield (%)
1	CH_3SO_2	**24a**	34
2	(p-CH_3)–C_6H_4–SO_2	**24b**	32
3	CH_3CO	**24c**	31
4	PhCO	**24d**	30
5	PhCH=CHCO	**24e**	22
6	BOC	**24f**	45
7	Cbz	**24g**	56
8	(o-CHO)–C_6H_4–CO	**24h**	31

Table 8 Reactivity of N-protected thiazolidines



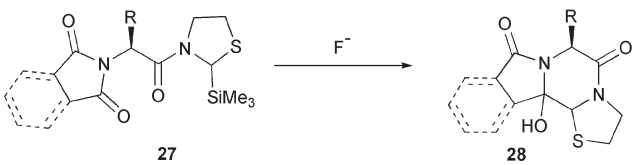
24 **25**

Entry	PG	R	Yield (%)
1	Mesyl	Ph	52
2	Tosyl	PhCHO	43
3	Acetyl	PhCHO	30
4	Acetyl	p-NO_2–C_6H_4–CHO	35
5	Boc	PhCHO	50
6	Boc	2-thienyl–CHO	41



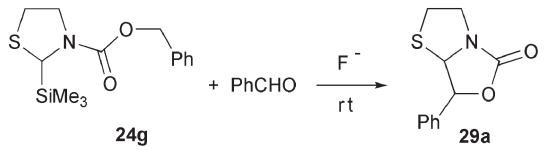
24h **26**

Scheme 6



27
R = Me, $CH_2CH(CH_3)_2$, CH_2Ph **28**

Scheme 7



24g 29a

Scheme 8

A different behaviour was observed when the protecting group was Cbz. In that case, under the same experimental conditions, a clean cyclization to oxazolidinones was observed (Scheme 8).[84]

In fact, by reacting Cbz-substituted 2-trimethylsilyl-1,3-thiazolidine **24g** with benzaldehyde at rt under fluoride ion catalysis, no trace of the expected adduct was observed, but oxazolidinone **29a** was isolated as the sole product as a 1 : 1 mixture of diastereoisomers (Scheme 8), probably arising from intramolecular attack by the alcoholate intermediate on the Cbz carbonyl carbon.

A similar behaviour was observed by Gawley *et al.* in the reaction of *N*-Boc 2-lithio-4-isopropyl-1,3-thiazolidine with pivalaldehyde and cyclohexylaldehyde, which led to the formation of the oxazolidinones, while on the contrary, the reaction with benzaldehyde afforded only the open chain adduct.[25]

When we looked for a generalization in such behaviour, the reactivity proved not to be straightforward, but to be a function of the temperature and the nature of the aldehyde; higher temperatures favoring the bicyclic compounds and lower ones leading to predominantly open chain adducts.

Thus, for instance, benzaldehyde, *para*-fluorobenzaldehyde, butyrraldehyde and cyclohexylaldehyde (Table 9, entries 1–4) at rt gave the bicyclic compounds **29** exclusively, while *para*-trifluoro- and *para*-nitrobenzaldehyde (Table 9, entries 5 and 6) gave only the open chain adducts **30**. 2-Thienyl- and *para*-anisaldehyde, on the contrary, gave mixtures of both products **29** and **30** (Table 9, entries 7 and 8). The reactivity thus appears to be clearly temperature dependent, in that higher temperatures (35 °C) were shown to favour cyclization, while lower ones gave open chain adducts. Interestingly, the *syn*-adduct was shown to undergo cyclization faster that the *anti*-adduct, leading to an interesting kinetic resolution. As an example, thiophene-2-carbaldehyde at rt led to the isolation of a mixture of cyclic compounds **29** (*syn* : *anti* 80 : 20), together with the α-hydroxy thiazolidines **30** (Table 9, entry 7). These latter compounds were isolated as single diastereoisomers with an *anti*-configuration, while the fused oxazolidinones **29** appeared as a 80 : 20 mixture of *syn*- and *anti*-isomers, as determined by NMR analysis.

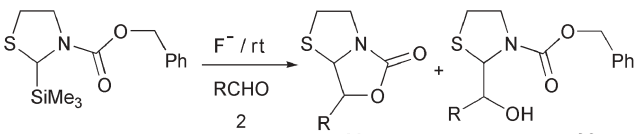
The **29** : **30** overall ratio, determined at the end of the reaction, was 65 : 35 (Table 9, entry 7).

Such results can be best explained by a faster intramolecular cyclization rate for the *syn*-hydroxy thiazolidine with respect the isomeric *anti*-adduct.

A similar behaviour was also evident for *para*-methoxybenzaldehyde (Table 9, entry 8).

Once the general behaviour of thiazolidine reactivity had been established, the stereochemical aspect was taken into consideration and the reactivity of different substituted thiazolidines was considered.

Table 9 Reaction of thiazolidines with aldehydes



24g 29 30

Entry	Aldehyde	**29**	**30**	*T*	Yield (%)
1	PhCHO	100	0	rt	68
		65	35	0 °C	60
2	(*p*-F)–C_6H_4–CHO	100	0	rt	61
		65	35	0 °C	58
3	$CH_3(CH_2)_2CHO$	100	0	rt	32
		65	35	0 °C	31
4	Cy–CHO	100	0	rt	28
		65	35	0 °C	31
5	(*p*-CF_3)–C_6H_4–CHO	0	100	rt	37
		65	35	35 °C	42
6	(*p*-NO_2)–C_6H_4–CHO	0	100	rt	30
		65	35	35 °C	32
7	2-Thienyl–CHO	65	35	rt	43
		30	70	0 °C	46
		100	0	35 °C	51
		0	100	−20 °C	48
8	(*p*-MeO)–C_6H_4–CHO	65	35	rt	40
		100	0	−20 °C	41

Several substituted thiazolidines were synthesized, generally as a mixture of *cis*- and *trans*-isomers that could be chromatographically separated to afford the enantiopure compounds (Table 10).

Thus, for instance, both *trans*- (**31a**) and *cis*- (**31b**) diastereoisomers of 4-(isopropyl)-*N*-Boc-2-trimethylsilyl thiazolidine were synthesized and reacted with aldehydes to afford the expected products as a mixture of diastereoisomers (Table 10).[85] No diastereoselectivity is observed, but interestingly, the functionalization occurs with retention of configuration of the starting C–Si bond, thus affording a mixture of enantiopure diastereoisomers. In search of more generality, *cis*-5-methyl-2-trimethylsilyl thiazolidine (**34**) was also synthesized and reacted with several aldehydes (Table 11). Again, no diastereoselection was observed, only stereoconservative functionalization of the C–Si bond.

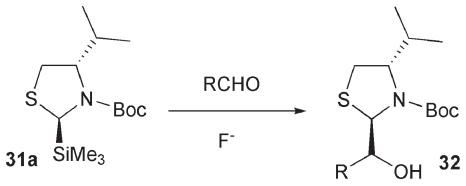
Silyl 1,3-oxathiolanes

As already mentioned, oxathioacetals are important derivatives that, together with acetals and dithioacetals, are the most commonly used protecting groups for carbonyl compounds.[86]

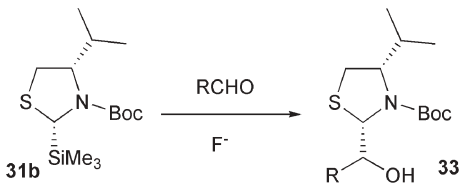
They can be employed as acyl anion equivalents in umpolung reactivity to form new C–C bonds,[86] while differently substituted chiral derivatives have been used in diastereoselective reactions.

Furthermore, the use of oxathioacetals is more convenient than their corresponding acetals or dithioacetals, being more

Table 10 Stereoselective functionalization of 4-isopropyl thiazolidine



Entry	R	Yield (%)
1	Ph	31
2	(*p*-CH_3O)–C_6H_4	36
3	2-Thienyl	35



Entry	R	Yield (%)
1	Ph	35
2	(*p*-CH_3O)–C_6H_4	38
3	2-Thienyl	35

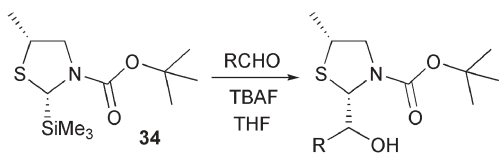
stable than O,O-acetals under acidic conditions and easier to deprotect than S,S-acetals.[10]

1,3-Oxathiolanes are also very interesting compounds, and several methods have been reported for their synthesis. Typical procedures involve the use of carbonyl compounds and 1,2-mercaptoalcohols under suitable catalytic conditions.[86,87]

In addition, this heterocyclic ring is contained in several pharmacologically active molecules. In fact, suitably substituted 1,3-oxathiolanes behave as muscarinic agents,[88] antiviral agents[89] and also show biological activity.[90]

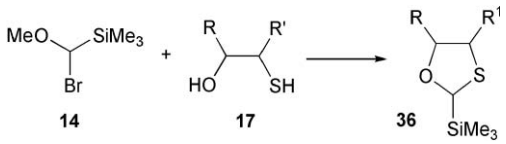
The methodology already used to access five-membered ring silylated heterocycles was also applied to obtain 2-silyl oxathiolanes through the reaction of β-mercaptoalcohols with bromo(methoxy)methyl trimethylsilane (**14**) in the presence of diisopropylethylamine, leading to the isolation of an open chain intermediate that could, nevertheless, be cyclized by adding concentrated HCl so as to obtain the desired silylated 1,3-oxathiolanes **36** (Table 12).[91]

Table 11 Reaction of 5-methyl thiazolidine



Entry	R	Yield (%)
1	Ph	28
2	(*p*-CH_3O)–C_6H_4	47
3	2-Thienyl	30
4	(*p*-F)–C_6H_4	25
5	(*p*-CF_3)–C_6H_4	34

Table 12 Synthesis of silyl oxathiolanes



Entry	R	R^1	Yield (%)
1	H	H	63
2	Me	H	75
3	Ph	H	61
4	$(Me)_2CHOCH_2$-	H	79
5	(2*R*)-CH_2OMe	H	54
6	(2*S*)-CH_2OCH_2Ph	H	71

The reaction was performed with 2-mercaptoethanol to obtain the unsubstituted oxathiolane (Table 12, entry 1) and also with β-mercaptoalcohols **17** bearing different substituents, leading to the synthesis of 5-substituted-2-silyl-1,3-oxathiolanes **36** (Table 12, entries 2–6).

These 5-substituted oxathiolanes were isolated as a mixture of diastereoisomers that could be chromatographically separated. It is interesting to observe that the dr was usually up to 4 : 1. When enantiopure 1,2-mercaptoalcohols were reacted (Table 12, entries 5 and 6), chiral oxathiolanes were obtained as *cis*- and *trans*-isomers, the *cis*-derivative usually being the major diastereoisomer.

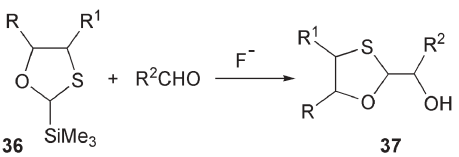
Reaction with aldehydes allowed the nucleophilic transfer of the oxathiolane moiety, leading to the corresponding functionalized α-hydroxy oxathiolanes **37** (Table 13), so revealing a smooth functionalization of such heterocyclic rings under mild basic conditions and the generation of a novel class of acyl anion synthons.[43]

Reaction again occurred in the presence of anhydrous TBAF, which in our hands was demonstrated to be the most efficient way of promoting the transformation.

No appreciable diastereoselectivity was evident but a stereoconservative functionalization was obtained when chiral oxathiolanes were used.

The functionalization seemed rather general and occurred with different aromatic and heteroaromatic aldehydes, leading to the synthesis of a representative number of homologous α-hydroxy aromatic and heteroaromatic aldehydes. No reaction was observed with non-enolizable aliphatic aldehydes, only the desilylated oxathiolane.[92]

Table 13 Reactivity of silyl oxathiolanes with aldehydes



Entry	R	R^1	R^2	Yield (%)
1	H	H	Ph	18
2	H	H	2-Thienyl	24
3	Me	H	Ph	72
4	Ph	H	Ph	22
5	(5*R*)-$MeOCH_2$	H	(*p*-F)–C_6H_4	48

Reactivity of silyl dioxolanes

1,3-Dioxolanes can be metalated, but in most cases the resulting anions are unstable and undergo fragmentation with elimination of an alkene to give the corresponding benzoates. 2-Aryl-substituted dioxolanes, on the contrary, can be deprotonated at the 2-position, thus acting as effective acyl anion equivalents.[14b,17,93]

2-Lithio dioxolanes can nevertheless be obtained through reductive lithiation or transmetalation of the corresponding stannane.[14b]

On the other hand, when 2-phenyl-2-trimethylsilyl-1,3-dioxolane (**38**) was reacted with different electrophiles in the presence of fluoride ion, a smooth transfer of the dithiolane moiety was obtained, thus showing that dioxolanes can also be efficiently functionalized under rather mild conditions, and providing evidence of another acyl anion synthon (Table 14).[94]

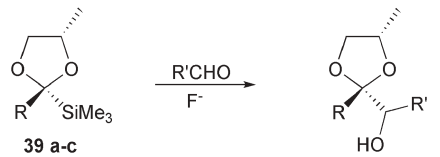
When stereodefined dioxolanes were taken into consideration, their behavior in reactions was shown to be quite different from the previously considered heterocycles, showing that, in the present case, stereoconservative carbodesilylation appears to be strictly dependent on the substituent present on the acetalic carbon and its ability to stabilize a carbanionic species. Thus 2-(*para*-methoxyphenyl)-2-trimethylsilyl-, 2-phenyl-2-trimethylsilyl- and 2-(*para*-trifluoromethylphenyl)-2-trimethylsilyl-4-methyl-1,3-dioxolanes were prepared, and the obtained *cis*- (**39a–c**) and *trans*- (**40a–c**) stereoisomers separated. Further reaction of the *cis*-diastereoisomer **39a** (R = (*p*-MeO)–C_6H_4) with 2-furylaldehyde (Table 15, entry 1) afforded, in 95% yield, an equimolar mixture of only two diastereoisomers, originating from the newly formed stereocenter, thus confirming a clean functionalization with retention of configuration. The corresponding *trans*-isomer **40a** (R = (*p*-MeO)–C_6H_4) behaved similarly, affording the corresponding adducts in a similar yield and with retention of configuration. On the other hand, when reacting both the *cis*- and *trans*-isomers **39b** and **40b** (R = Ph), respectively, with 2-furylaldehyde (Table 15, entries 2 and 6) and *para*-anisaldehyde (Table 15, entries 3 and 7), four stereoisomers, originating from the new stereocenter and epimerization, were obtained for each reaction in a ratio of 25 : 25 : 20 : 20, thus unequivocally showing that epimerization had occurred during the reaction. Furthermore, when both *cis*- and *trans*-diastereoisomers **39c** and **40c** (R = (*p*-CF_3)–C_6H_4), respectively, were similarly reacted (Table 15, entries 4 and 8), a yield of 85% was obtained from a mixture of, once again, four diastereoisomers, this time in an almost equimolar ratio, showing an even greater degree of epimerization.[94]

As seen above, 2-functionalized dioxolanes show a variable degree of epimerization, strictly depending on the nature of the substituent. Such behaviour does not hamper their use as acyl anion equivalents but poses some limits on their use in stereoselective synthesis.

Table 14 Functionalization of 2-phenyl-2-trimethylsilyl-1,3-dioxolane (**38**)

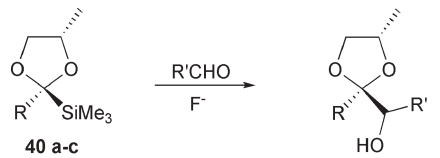
Entry	E	Yield (%)
1	$(CH_3)_2CHCHO$	50
2	$PhCOCH_3$	20
3	Cy–CHO	60
4	$PhCHCH_3CHO$	60
5	*n*-$C_5H_{11}CHO$	50
6	PhCH=CHCHO	67
7	CH_2=$CHCOCH_3$	53

Table 15 Reactivity of chiral dioxolanes



39 a-c

Entry	R	R′	Yield (%)
1	(*p*-MeO)–C_6H_4	2-furyl	95
2	Ph	2-furyl	88
3	Ph	(*p*-MeO)–C_6H_4	95
4	(*p*-CF_3)–C_6H_4	2-furyl	85



40 a-c

Entry	R	R′	Yield (%)
5	(*p*-MeO)–C_6H_4	2-furyl	95
6	Ph	2-furyl	88
7	Ph	(*p*-MeO)–C_6H_4	95
8	(*p*-CF_3)–C_6H_4	2-furyl	85

Silyl 1,3-oxazolidines

Oxazolidines have been used as chiral formyl anion equivalents for addition to aldehydes.[22] Thus, reactions of 2-stannyl-4,5-disubstituted oxazolidines undergo lithium–tin exchange[23] and addition to aldehydes, albeit with poor diastereoselectivity.

On the other hand, 2-trimethylsilyl-1,3-oxazolidine (**41**) was obtained by following the general protocol for the synthesis of five-membered ring silylated heterocycles through the reaction of **14** with a suitably N-protected 2-aminoethanol.

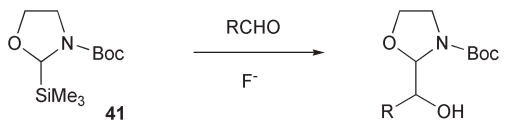
It has been found that the fluoride-induced reaction of *N*-Boc-protected 2-silyl-oxazolidine with aldehydes affords addition products of the oxazolidine and the formyl moiety as a 1 : 1 mixture of diastereoisomers (Table 16).[95]

On the contrary, the reaction performed at rt with *N*-Cbz-substituted oxazolidine and TBAF, in the presence of benzaldehyde and 2-thienyl aldehyde, led exclusively to the isolation of the cyclofused compounds, thus revealing a similar behaviour to the analogous silyl thiazolidine. In this case, also no appreciable diastereoselectivity was observed.[95]

Conclusions

Organosilanes have been widely used in the search for new synthetic methodologies. In this context, the fluoride

Table 16 Reactivity of *N*-Boc oxazolidines



Entry	R	Yield (%)
1	Ph	28
2	2-Thienyl	30
3	(*p*-F)–C_6H_5	25

ion-induced reactivity of a C–Si bond has for a long time been used in the generation of nucleophilic species under mild conditions, as testified, for instance, by the level of importance that the chemistry of allyl silanes has attained in recent years. Application of these concepts to a series of silyl heterocycles has led to the development of a simple and mild protocol for their not always obvious functionalization. Thus, for instance, while dithiolanes undergo cycloreversion under strongly basic conditions, silyl dithiolane can be efficiently functionalized, revealing a new synthetic equivalent of a dithiolane anion. Similarly, different heterocycles, such as oxathiolanes, dioxolanes, thiazolidines and oxazolidines, can be efficiently reacted under similar conditions, affording new classes of potential formyl and acyl anion synthons. An interesting feature of such reactivity appears to be its stereoconservative behaviour, which allows the transfer of stereochemical information from stereodefined molecules to the corresponding products during reactions.

A particular versatility was encountered in the thiazolidine series, which, depending on the protecting group present at nitrogen, may lead to the synthesis of open chain adducts, or, depending on the reaction conditions, to polycyclic derivatives with interesting degrees of diastereoselectivity, thus suggesting the possible fine tuning of such reactions.

Furthermore, due to the non-obvious accessibility of current silyl heterocycles, a novel protocol for their synthesis has been developed through the reactivity of bifunctional molecules, such as mercapto alcohols, dithiols and mercapto amines, with bromo(methoxy)methyl trimethylsilane.

Finally, as a further generalization, a simple and high yielding route to both racemic and stereodefined substituted mercapto alcohols, dithiols and mercapto amines, useful building blocks in the synthesis of the current heterocycles, has been developed.

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References

1 T. A. Hase, *Umpoled Synthons: A Survey of Sources and Uses in Synthesis*, Wiley Interscience, New York, 1987.
2 (*a*) P. J. Kocienski, *Tetrahedron Lett.*, 1980, **21**, 1559; (*b*) D. J. Ager and M. B. East, *J. Org. Chem.*, 1986, **51**, 3983.
3 J. Otera, Y. Niibo and H. Nozaki, *J. Org. Chem.*, 1989, **54**, 5003.
4 T. Cohen and S. M. Nolan, *Tetrahedron Lett.*, 1978, 3533.
5 D. J. Ager, J. E. Gano and S. I. Parekh, *J. Chem. Soc., Chem. Commun.*, 1989, 1256.
6 S. Sengupta and V. Snieckus, *J. Org. Chem.*, 1990, **55**, 5680.
7 (*a*) D. Enders, J. Vazquez and G. Raabe, *Eur. J. Org. Chem.*, 2000, 893; (*b*) R. Fernandez and J. M. Lassaletta, *Synlett*, 2000, 1228.
8 H. Nemoto, Y. Kubota and Y. Yamamoto, *J. Org. Chem.*, 1990, **55**, 4515.
9 (*a*) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 639; (*b*) D. Seebach and E. J. Corey, *J. Org. Chem.*, 1975, **40**, 231; (*c*) B.-T. Gröbel and D. Seebach, *Synthesis*, 1977, 357; (*d*) N. H. Andersen, D. A. Mc Crae, D. B. Grotjahn, S. Y. Gabhe, L. J. Theodore, R. M. Ippolito and T. K. Sarkar, *Tetrahedron*, 1981, **37**, 4068; (*e*) P. C. B. Page, M. B. van Niel and J. C. Prodger, *Tetrahedron*, 1989, **45**, 7643.
10 (*a*) P. J. Kocieński, *Protecting Groups*, Georg Thieme, Stuttgart, 3rd edn, 1994, pp. 171; (*b*) E. Burghardt, *J. Sulfur Chem.*, 2005, **26**, 411 and references cited therein.
11 (*a*) E. L. Eliel, A. A. Hartmann and A. G. Abatjoglou, *J. Am. Chem. Soc.*, 1974, **96**, 1807 and references cited therein; (*b*) A. G. Abatjoglou, E. L. Eliel and L. F. Kuyper, *J. Am. Chem. Soc.*, 1977, **99**, 8262 and references cited therein.
12 (*a*) S. R. Wilson, G. M. Georgiadis, H. N. Khatri and J. E. Bartmess, *J. Am. Chem. Soc.*, 1980, **102**, 3577; (*b*) S. R. Wilson, P. Caldera and M. A. Jester, *J. Org. Chem.*, 1982, **47**, 3319; (*c*) T. Oida, S. Tanimoto, H. Terao and M. Okano, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1715.
13 (*a*) J. E. Lynch and E. L. Eliel, *J. Am. Chem. Soc.*, 1984, **106**, 2943; (*b*) K. Fuji, M. Ueda, K. Sumi, K. Kajiwara, E. Fujita, T. Iwashita and I. Miura, *J. Org. Chem.*, 1985, **50**, 657; (*c*) E. L. Eliel, E. Lynch, F. Kume and S. V. Frye, *Org. Synth.*, 1987, **65**, 215; (*d*) E. L. Eliel, X. Bai, A. F. Abdel-Magid and R. O. Hutchins, *J. Org. Chem.*, 1990, **55**, 4951; (*e*) K. Utimoto, T. Kodama and S. Matsubara, *Synlett*, 1995, 501.
14 (*a*) K. J. H. Kruithof, R. F. Schmitz and G. W. Klumpp, *Tetrahedron*, 1983, **39**, 3073; (*b*) C. S. Shiner, T. Tsunoda, B. A. Goodman, S. Ingham, S. Lee and P. E. Vorndam, *J. Am. Chem. Soc.*, 1989, **111**, 1381; (*c*) D. Enders, J. Kirchoff, D. Mannes and G. Raabe, *Synthesis*, 1995, 659; (*d*) M.-C. Roux, L. Wartski, M. Nierlich and M. Lance, *Tetrahedron*, 1996, **52**, 10083.
15 R. A. Aitken and A. W. Thomas, in *Advances in Heterocyclic Chemistry*, ed. A. R. Katritzky, Academic Press, New York, 2001, vol. **79**, pp. 89 and references cited therein.
16 (*a*) P. C. B. Page, M. J. McKenzie and D. R. Buckle, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2673; (*b*) P. C. B. Page, M. Purdie and D. Lathbury, *Tetrahedron Lett.*, 1996, **37**, 8929; (*c*) V. K. Aggarwal, A. Thomas and S. Schade, *Tetrahedron*, 1997, **53**, 16213; (*d*) V. K. Aggarwal, S. Schade and H. Adams, *J. Org. Chem.*, 1997, **62**, 1139.
17 (*a*) R. A. Aitken and A. W. Thomas, *Synlett*, 1998, 102; (*b*) R. A. Aitken, S. D. McGill and L. A. Power, *ARKIVOC*, 2006, **vii**, 292.
18 G. W. Gokel, W. Gerdes, D. E. Miles, J. M. Hufnal and G. A. Zerby, *Tetrahedron Lett.*, 1979, **20**, 3375.
19 (*a*) A. R. Katritzky, Z. Yang and J. N. Lam, *J. Org. Chem.*, 1991, **56**, 2143; (*b*) A. R. Katritzky, H. Lang, Z. Wang and Z. Lie, *J. Org. Chem.*, 1996, **61**, 7551; (*c*) A. R. Katritzky, D. Feng and H. Lang, *J. Org. Chem.*, 1997, **62**, 706; (*d*) A. R. Katritzky, Z. Wang, H. Lang and D. Feng, *J. Org. Chem.*, 1997, **62**, 4125; (*e*) A. R. Katritzky, D. Feng and M. Qi, *J. Org. Chem.*, 1998, **63**, 1473.
20 R. E. Gawley, S. A. Campagna, M. Santiago and T. Ren, *Tetrahedron: Asymmetry*, 2002, **13**, 29.
21 (*a*) C. Gaul, K. Scharer and D. Seebach, *J. Org. Chem.*, 2001, **66**, 3059; (*b*) C. Gaul and D. Seebach, *Helv. Chim. Acta*, 2002, **85**, 772.
22 N. Kise, T. Urai and J.-c. Yoshida, *Tetrahedron: Asymmetry*, 1998, **9**, 3125.
23 (*a*) L. Colombo, M. Di Giacomo, G. Brusotti and G. Delogu, *Tetrahedron Lett.*, 1994, **35**, 2063; (*b*) L. Colombo and M. Di Giacomo, in *Current Trends in Organic Synthesis*, ed. C. Scolastico and F. Nicotra, 1999, pp. 171.
24 (*a*) L. Wang, S. Nakamura and T. Toru, *Org. Biomol. Chem.*, 2004, **2**, 2168; (*b*) L. Wang, S. Nakamura, Y. Ito and T. Toru, *Tetrahedron: Asymmetry*, 2004, **15**, 3059.

25 R. E. Gawley, Q. Zhang and A. T. McPhail, *Tetrahedron: Asymmetry*, 2000, **11**, 2093.
26 A. I. Meyers, P. D. Edwards, W. F. Rieker and T. R. Bailey, *J. Am. Chem. Soc.*, 1984, **106**, 3270.
27 A. Dondoni, *Pure Appl. Chem.*, 1990, **62**, 643.
28 (*a*) A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici and P. Pedrini, *J. Org. Chem.*, 1988, **53**, 1748; (*b*) A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici and P. Pedrini, *J. Org. Chem.*, 1989, **54**, 693; (*c*) A. Dondoni, A. W. Douglas and I. Shinkai, *J. Org. Chem.*, 1993, **58**, 3196; (*d*) A. Dondoni, *Synthesis*, 1998, 1681.
29 E. L. Eliel, *Tetrahedron*, 1974, **30**, 1503.
30 (*a*) A. Krief and L. Defrere, *Tetrahedron Lett.*, 1996, **37**, 2667; (*b*) A. Krief and L. Defrere, *Tetrahedron Lett.*, 1996, **37**, 8011.
31 A. Krief and L. Defrere, *Tetrahedron Lett.*, 1996, **37**, 8015.
32 (*a*) S. E. Denmark and N. G. Almstead, *J. Org. Chem.*, 1994, **59**, 5130; (*b*) R. Corriu, *Pure Appl. Chem.*, 1988, **60**, 99; (*c*) T. H. Chan and I. Fleming, *Synthesis*, 1979, 761.
33 T. Dubuffet, R. Sauvetreand and J. F. Normant, *Tetrahedron Lett.*, 1988, **29**, 5923.
34 (*a*) W. S. Palmer and K. A. Woerpel, *Organometallics*, 1997, **16**, 1097; (*b*) J. T. Shaw and K. A. Woerpel, *J. Org. Chem.*, 1997, **62**, 442; (*c*) P. M. Bodnar, W. S. Palmer, J. T. Shaw, J. H. Smitrovich, J. D. Sonnenberg, A. L. Presley and K. A. Woerpel, *J. Am. Chem. Soc.*, 1995, **117**, 10575 and references cited therein.
35 T. Hatanaka and T. Hiyama, *J. Am. Chem. Soc.*, 1990, **112**, 7793.
36 E. J. Corey and Z. Chen, *Tetrahedron Lett.*, 1994, **35**, 8731.
37 P. McDougall and B. D. Condon, *Tetrahedron Lett.*, 1989, **30**, 789.
38 S. Thayumanavan, Y. S. Park, P. Farid and P. Beak, *Tetrahedron Lett.*, 1997, **38**, 5429.
39 V. K. Aggarwal and M. Ferrara, *Org. Lett.*, 2000, **2**, 4107.
40 V. Cerè, A. Capperucci, A. Degl'Innocenti and S. Pollicino, *Tetrahedron Lett.*, 2006, DOI: 10.1016/j.tetlet.2006.08.078.
41 (*a*) H. Paulsen, W. Koebernick and H. Koebernick, *Tetrahedron Lett.*, 1976, **17**, 2297; (*b*) M. Yamashita and R. Suemitsu, *J. Chem. Soc., Chem. Commun.*, 1977, 691.
42 (*a*) F. H. Elsner, H. G. Woo and T. D. Tilley, *J. Am. Chem. Soc.*, 1988, **110**, 313; (*b*) J. A. Soderquist and E. I. Miranda, *J. Am. Chem. Soc.*, 1992, **114**, 10078.
43 A. Capperucci, G. Castagnoli, A. Degl'Innocenti, I. Malesci and T. Nocentini, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 1297.
44 (*a*) A. Degl'Innocenti and A. Capperucci, *Eur. J. Org. Chem.*, 2000, 2171; (*b*) A. Degl'Innocenti, A. Capperucci, G. Castagnoli and I. Malesci, *Synlett*, 2005, 1965.
45 *Inter alia*: (*a*) W. Lidy and W. Sundermeyer, *Tetrahedron Lett.*, 1973, **14**, 1449; (*b*) J. C. Mullis and W. P. Weber, *J. Org. Chem.*, 1982, **47**, 2873; (*c*) T. L. Guddenheim, *J. Am. Chem. Soc.*, 1982, **104**, 5849; (*d*) P. G. Gassman and R. S. Gremban, *Tetrahedron Lett.*, 1984, **25**, 3259; (*e*) C. H. Behrens and K. B. Sharpless, *J. Org. Chem.*, 1985, **50**, 5696; (*f*) H. Yamashita, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 1213; (*g*) J. Iqbal, A. Pandey, A. Shukla, R. R. Srivastava and S. Tripathi, *Tetrahedron*, 1990, **46**, 6423 and references cited therein; (*h*) V. Kesavan, D. Bonnet-Delpon and J.-P. Bégué, *Tetrahedron Lett.*, 2000, **41**, 2895 and references cited therein.
46 *Inter alia*: (*a*) J. M. Lalancette and A. Frêche, *Can. J. Chem.*, 1971, **49**, 4047; (*b*) A. E. Vougioukas and H. B. Kagan, *Tetrahedron Lett.*, 1987, **28**, 6065; (*c*) T. Nishikubo, T. Iizawa, M. Shimojo, T. Kato and A. Shiina, *J. Org. Chem.*, 1990, **55**, 2536; (*d*) M. Chini, P. Crotti, E. Giovani, F. Macchia and M. Pineschi, *Synlett*, 1992, 303; (*e*) D. Albanese, D. Landini and M. Penso, *Synthesis*, 1994, 34; (*f*) W.-C. Chou, L. Chen, J.-M. Fang and C.-H. Wong, *J. Am. Chem. Soc.*, 1994, **116**, 6191; (*g*) T. Iida, Y. Yamamoto, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1997, **119**, 4783; (*h*) M. H. Wu and E. N. Jacobsen, *J. Org. Chem.*, 1998, **63**, 5252; (*i*) J. Wu, X.-L. Hou, L.-X. Dai, L.-J. Xia and M.-H. Tang, *Tetrahedron: Asymmetry*, 1998, **9**, 3431; (*j*) J. S. Yadav, B. V. Reddy and G. Baishya, *Chem. Lett.*, 2002, 906; (*k*) F. Friguelli, F. Pizzo, S. Tortoioli and L. Vaccaro, *Tetrahedron Lett.*, 2003, **44**, 6785; (*l*) B. Movassagh, S. Sobhani, F. Kheirdoush and Z. Fadaei, *Synth. Commun.*, 2003, **33**, 3103; (*m*) H. Heimgartner, C. Fu, M. Blagoev and A. Linden, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 1309.
47 (*a*) E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson and S. Hammarstrom, *J. Am. Chem. Soc.*, 1980, **102**, 1436; (*b*) E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson and S. Hammarstrom, *J. Am. Chem. Soc.*, 1980, **102**, 3663; (*c*) J. Rokach, Y. Girard, Y. Guindon, J. G. Atkinson, M. Larue, R. N. Young, P. Masson and G. Holme, *Tetrahedron Lett.*, 1980, **21**, 1485.
48 (*a*) K. Paulvannan and T. Chen, *Synlett*, 1999, 1371; (*b*) A. Mühlman, B. Classon, A. Hallberg and B. Samuelsson, *J. Med. Chem.*, 2001, **44**, 3402.
49 (*a*) Y. Guindon, R. N. Young and R. Frenette, *Synth. Commun.*, 1981, **11**, 391; (*b*) Y. Tanabe, K. Mori and Y. Yoshida, *J. Chem. Soc., Perkin Trans. 1*, 1997, 671; (*c*) J. Brittain and Y. Gareau, *Tetrahedron Lett.*, 1993, **34**, 3363; (*d*) E. W. Abel and D. J. Walker, *J. Chem. Soc. A*, 1968, 2338; (*e*) B. M. Trost and T. S. Scanlan, *Tetrahedron Lett.*, 1986, **27**, 4141.
50 (*a*) B. N. Steger, *U. S. Patent*, 4564710, appl. 84-669558, 1986; B. N. Steger, *Chem. Abs.*, 1986, **105**, 45235; (*b*) H. Morishiri, K. Shimakawa, A. Ryu, N. Kawato and S. Kobayashi, *Jpn. Kokai Tokkyo Koho*, 2003, JP 2003155269; H. Morishiri, K. Shimakawa, A. Ryu, N. Kawato and S. Kobayashi, *Chem. Abs.*, 2004, **138**, 385064.
51 F. G. Bordwell and H. M. Anderson, *J. Am. Chem. Soc.*, 1953, **75**, 4959.
52 J. C. Justo de Pomar and J. A. Soderquist, *Tetrahedron Lett.*, 1998, **39**, 4409.
53 A. Degl'Innocenti, A. Capperucci, A. Cerreti, S. Pollicino, S. Scapecchi, I. Malesci and G. Castagnoli, *Synlett*, 2005, 3063.
54 A. Degl'Innocenti, A. Capperucci, T. Nocentini, G. Castagnoli, I. Malesci and A. Cerreti, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 1247.
55 (*a*) P. N. Guivisdalsky and R. Bittman, *J. Am. Chem. Soc.*, 1989, **111**, 3077; (*b*) R. M. Hanson, *Chem. Rev.*, 1991, **91**, 437; (*c*) M.-J. Kim and Y. K. Choi, *J. Org. Chem.*, 1992, **57**, 1605.
56 *Inter alia*: (*a*) W. McCoull and F. A. Davis, *Synthesis*, 2000, 1347; (*b*) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (*c*) A. Padwa and S. Murphree, *ARKIVOC*, 2006, **iii**, 6.
57 (*a*) R. Ingenitio, E. Bianchi, D. Fattori and A. Pressi, *J. Am. Chem. Soc.*, 1999, **121**, 11369; (*b*) B. Adams, K. J. M. Beresford, S. M. Whyte and D. M. Young, *Chem. Commun.*, 2000, 619 and references cited therein.
58 T. Katagiri, M. Takahashi, Y. Fujiwara, H. Ihara and K. Uneyama, *J. Org. Chem.*, 1999, **64**, 7323.
59 (*a*) K. Nakajiima, H. Oda and K. Okawa, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 520; (*b*) O. Ploux, M. Caruso, G. Chassaing and A. Marquet, *J. Org. Chem.*, 1988, **53**, 3154; (*c*) J. Legters, J. G. H. Willems, L. Thijs and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas*, 1992, **111**, 59; (*d*) L. Antolini, M. Bucciarelli, E. Caselli, P. Davoli, A. Forni, I. Moretti, F. Prati and G. Torre, *J. Org. Chem.*, 1997, **62**, 8784; (*e*) B. Crousse, S. Narizuka, D. Bonnet-Delpon and J.-P. Begue, *Synlett*, 2001, 679; (*f*) C. Xiong, W. Wang, C. Cai and V. J. Hruby, *J. Org. Chem.*, 2002, **67**, 1399.
60 J. Wu, X.-L. Hou and L.-X. Dai, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1314.
61 G. Righi and S. Catullo, *Synth. Commun.*, 2004, **34**, 85.
62 R.-H. Fan and X. L. Hou, *J. Org. Chem.*, 2003, **68**, 726.
63 P. E. Maligres, M. M. See, D. Askin and P. J. Reider, *Tetrahedron Lett.*, 1997, **38**, 5253.
64 (*a*) J. Wu, X.-L. Dai Hou and L.-X. Dai, *J. Org. Chem.*, 2000, **65**, 1344; (*b*) S. Minataka, Y. Okada, Y. Oderaotoshi and M. Komatsu, *Org. Lett.*, 2005, **7**, 3509 and references cited therein.
65 M. G. Silvestri and C.-H. Wong, *J. Org. Chem.*, 2001, **66**, 910.
66 (*a*) Y. Usui, J. Noma, M. Hirano and S. Komiya, *J. Chem. Soc., Dalton Trans.*, 1999, 4397; (*b*) N. Iranpoor, H. Firouzabadi and A. A. Jafari, *Synth. Commun.*, 2003, **33**, 2321.
67 N. V. Schwartz, *J. Org. Chem.*, 1968, **33**, 2895.
68 A. Capperucci, A. Degl'Innocenti, A. Castagnoli and M. Acciai, *Tetrahedron*, submitted for publication.
69 J. L. Herrmann, J. E. Richman and R. H. Schlessinger, *Tetrahedron Lett.*, 1973, **14**, 2599.
70 S. Ncube, A. Pelter, K. Smith, P. Blatcher and S. Warren, *Tetrahedron Lett.*, 1978, **19**, 2345.
71 A. Degl'Innocenti, A. Capperucci and T. Nocentini, *Tetrahedron Lett.*, 2002, **42**, 4557.
72 A. Capperucci, V. Ceré, A. Degl'Innocenti, T. Nocentini and S. Pollicino, *Synlett*, 2002, 3063.

73 H. T. Clarke, J. R. Johnson and R. Robinson, *The Chemistry of Penicillins*, Princeton University Press, Princeton, NJ, 1949.
74 (*a*) R. D. Westland, R. A. Cooley, Jr., J. H. Holmes, J. S. Hong, M. H. Lin and M. L. Zwiesier, *J. Med. Chem.*, 1973, **16**, 319; (*b*) R. D. Westland, M. H. Lin, R. A. Cooley, Jr., M. L. Zwiesier and M. M. Grenan, *J. Med. Chem.*, 1973, **16**, 328; (*c*) P. S. Farmer, C. Leung and E. M. K. Lui, *J. Med. Chem.*, 1973, **16**, 411.
75 (*a*) H. T. Nagasawa, D. J. W. Goon, W. P. Muldoon and R. T. Zera, *J. Med. Chem.*, 1984, **27**, 591; (*b*) A. Wonacott, R. Cooke, F. R. Hayes, M. M. Hann, H. Jhoti, P. McMeekin, A. Mistry, P. G. B. Murray-Rust, O. M. P. Singh and M. P. Weir, *J. Med. Chem.*, 1993, **36**, 3113; (*c*) J. Samanen, T. Cash, D. Narindray, E. Brandeis, W. Adams, Jr, H. Weidemann and T. Yellin, *J. Med. Chem.*, 1991, **34**, 3036.
76 J. Kitchin, D. Holmes, D. Humber, R. Storer, S. Dolan, M. Hann, P. McMeekin and P. G. B. Murray-Rust, *World Patent*, WO9301174 A, 1992.
77 P. Faury, M. Camplo, A.-S. Charvet, N. Mourier, P. Barthelemy, J.-C. Graciet and J.-L. Kraus, *J. Heterocycl. Chem.*, 1994, **31**, 1465.
78 C. A. Gandolfi, R. Di Domenico, S. Spinelli, L. Gallico, L. Fiocchi, A. Lotto, E. Menta, A. Borghi, C. Dalla Rosa and S. Tornella, *J. Med. Chem.*, 1995, **38**, 508.
79 O. Dubs, H. Kuentzel, M. Pesaro and H. Schmidt, *Swiss Patent*, CA 87:201514, 1977.
80 J. C. Sheenan and D. H. Yang, *J. Am. Chem. Soc.*, 1958, **80**, 1158.
81 (*a*) L. J. Altman and S. L. Richeimer, *Tetrahedron Lett.*, 1971, 4709; (*b*) A. I. Meyers, R. Munavu and J. Durandetta, *Tetrahedron Lett.*, 1972, 3929; (*c*) T. Okutome, Y. Sakurai, M. Kurumi, H. Kaeamura, S. Sato and K. Yamaguchi, *Chem. Pharm. Bull.*, 1975, **23**, 48.
82 (*a*) P. Blondeau, C. Berse and D. Gravel, *Can. J. Chem.*, 1967, **45**, 49; (*b*) E. L. Eliel, E. U. Della and M. M. Rogic, *J. Am. Chem. Soc.*, 1959, **81**, 4322; (*c*) J. J. Herak, M. Kovacevic and B. Gaspert, *Croat. Chim. Acta*, 1977, **49**, 141.
83 A. Capperucci, A. Degl'Innocenti, T. Nocentini, A. Mordini, S. Biondi and A. Mordini, *Lett. Org. Chem.*, 2004, **1**, 55.
84 A. Degl'Innocenti, A. Capperucci, I. Malesci, G. Castagnoli, M. Acciai, T. Nocentini and S. Pollicino, *Synlett*, 2006, 2439.
85 A. Degl'Innocenti, A. Capperucci, I. Malesci and S. Pollicino, unpublished results.
86 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, 3rd edn, 1999, pp. 329.
87 For recent papers, see: (*a*) B. Karimi and H. Seradaj, *Synlett*, 2000, 805; (*b*) E. Mondal, P. R. Sahu, G. Bose and A. T. Khan, *Tetrahedron Lett.*, 2002, **43**, 2843; (*c*) R. Ballini, G. Bosica, R. Maggi, A. Mazzacani, P. Righi and G. Sartori, *Synthesis*, 2001, 1826.
88 (*a*) P. A. Lehmann, *Chirality*, 1990, **2**, 211; (*b*) S. Dei, C. Bellucci, M. Buccioni, M. Ferraroni, F. Gualtieri, L. Guandalini, D. Manetti, R. Matucci, M. N. Romanelli, S. Scapecchi and E. Teodori, *Bioorg. Med. Chem.*, 2003, **11**, 3153.
89 (*a*) N. Nguyen-Ba, N. Lee, L. Chan and B. Zacharie, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2223; (*b*) T. S. Mansour and H. Jin, *U. S. Patent*, 718555, 2001; T. S. Mansour and H. Jin, *Chem. Abs.*, 2001, **134**, 336206; (*c*) B. Belleau, P. Belleau and N. Nguyen-Ba, *U. S. Patent*, 98-172848, 2001; B. Belleau, P. Belleau and N. Nguyen-Ba, *Chem. Abs.*, 2001, **135**, 211232; (*d*) A. Kocabalkanli and R. F. Schinazi, *Farmaco*, 2002, **57**, 993.
90 (*a*) H. L. Holland and B. Munoz, *Can. J. Chem.*, 1988, **66**, 2299; (*b*) H. Ead, M. A. Abdelaziz and N. H. Metwalli, *Pol. J. Chem.*, 1991, **65**, 1291.
91 Due to the instability of these heterocycles under acidic conditions, it is convenient to emphasis that the treatment with HCl must not be for longer than 1 h 30 min. In fact, if the intermediate product is treated under acidic conditions for longer times, the fragmentation of the oxathiolane ring is observed.
92 A. Degl'Innocenti, A. Capperucci, A. Cerreti and S. Pollicino, unpublished results.
93 A. I. Meyers, A. L. Campbell, A. G. Abatjoglou and E. L. Eliel, *Tetrahedron Lett.*, 1979, 4159.
94 A. Degl'Innocenti, A. Capperucci and S. Pollicino, unpublished results.
95 A. Degl'Innocenti, A. Capperucci, I. Malesci and S. Pollicino, unpublished results.