



## Accepted Article

**Title:** 1,4-Dithiane-2,5-diol: An Attractive Platform for the Synthesis of Sulfur Containing Functionalized Heterocycles

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**To be cited as:** *Eur. J. Org. Chem.* 10.1002/ejoc.201701785

**Link to VoR:** <http://dx.doi.org/10.1002/ejoc.201701785>

# 1,4-Dithiane-2,5-diol: An Attractive Platform for the Synthesis of Sulfur Containing Functionalized Heterocycles

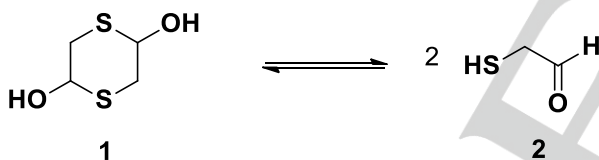
Francesco Zamberlan,<sup>[a]</sup> Anna Fantinati,<sup>[b]</sup> Claudio Trapella<sup>\*[b]</sup>

Dedicated to Professor Simonetta Benetti on the occasion of her retirement

**Abstract:** This microreview highlights the utility of 1,4-dithiane-2,5-diol **1** as a source for the in situ generation of 2-mercaptoacetaldehyde **2**, a versatile two-carbon synthon featuring both electrophilic and nucleophilic reaction centers widely utilized as an attractive platform for the preparation of sulfur-containing molecules. We discussed the involved chemistry, mainly focusing on its applications to the construction of sulfur-containing heterocyclic compounds including the thiophene and 1,3-thiazole families and other different sulfur-nitrogen and sulfur-oxygen heterocycles which continue to be a pillar of organic synthesis as a result of their broad application in organic and medicinal chemistry.

## 1. Introduction

The development of highly efficient synthetic methods to access sulfur-containing heterocycles, privileged structural units featuring many biologically active natural and synthetic compounds, is particularly appealing.<sup>[1,2]</sup> Compared with other starting materials, 1,4-dithiane-2,5-diol, **1**, the dimer of mercaptoacetaldehyde **2**, has emerged as an attractive platform for the preparation of these frameworks (Scheme 1).



Scheme 1 Formation of 2-mercaptoacetaldehyde from 1,4-dithiane-2,5-diol.

Indeed, the bifunctional nature of mercaptoacetaldehyde **2**, easily released in situ by treatment with tertiary amines or certain organocatalysts from the dimeric hemithioacetal **1**, could take part as a versatile two-carbon synthon in a variety of domino thia-Michael/aldol reactions. This microreview describes the chemistry of 1,4-dithiane-2,5-diol, mainly focusing on its applications to the construction of different sulfur-containing heterocycles, including tetrahydrothiophene, dihydrothiophene and thiophene derivatives as well as 1,3-thiazole and

thiazolidine derivatives, 1,3-oxathiolanes, tetrahydropyrans and other sulfur-nitrogen and sulfur-oxygen heterocyclic compounds. Indeed, 1,4-dithiane-2,5-diol **1** has been and continues to be widely used in organic synthesis, its utilization being greatly facilitated by the commercial availability.

Claudio Trapella was born in Ferrara in 1972, completed his PhD in pharmaceutical sciences in 2002 and is now assistant professor of organic chemistry. The main research interests are focused in the organotransition metal chemistry for the synthesis of biological active compounds especially in the pain field.



Anna Fantinati was born in Rovigo in 1990. She is a PhD student in organic chemistry and her main research interests are focused in the synthesis of bio-active spiro-compounds mitochondria target.



Francesco Zamberlan was born in Ferrara in 1984, and obtained his PhD in chemical sciences in 2013 from the University of Ferrara. After a few years of postdoctoral work at the University of Nottingham, he is now a lecturer in Organic Chemistry at the University of Lincoln. His research interests are in the field of chemical biology and bioimaging.



## 2. The Thiophene family

Thiophene derivatives, as well as the partially reduced 2,3- or 2,5-dihydrothiophene, or the totally reduced tetrahydrothiophene ring systems, are unique sulfur-containing heterocycles that have attracted a lot of attention, particularly because of their special place as natural products' building blocks.<sup>[1,2]</sup>

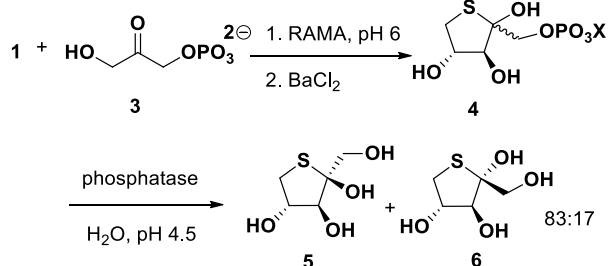
### 2.1 Tetrahydrothiophene synthesis

Tetrahydrothiophenes are important motifs in the context of natural as well as non-natural, biologically active compounds,

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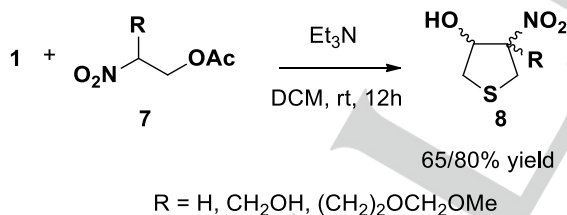
and materials chemistry.<sup>[1,2]</sup> In 1992, Effenberger and co-workers described an approach to 5-thio-*D*-xylulofuranoses **5** and **6** using rabbit muscle aldolase- (RAMA)-catalyzed reaction of mercaptoacetaldehyde with dihydroxyacetonephosphate **3**, which is likely the first utilization of 1,4-dithiane-2,5-diol **1** for the synthesis of the tetrahydrothiophene moiety.<sup>[3]</sup> After the initial aldol reaction, the product **4** was dephosphorylated by means of an acid phosphatase (Scheme 2).



Scheme 2: First utilisation of **1** in the synthesis of tetrahydrothiophenes.

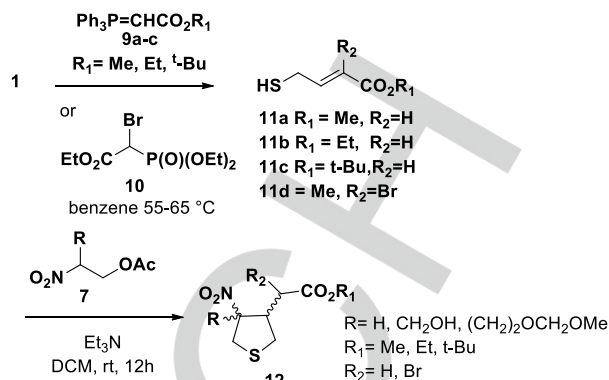
Later, the construction of tetrahydrothiophen-3-ol derivatives focused on the use of **1** as a versatile two-carbon synthon able to readily take part in [3+2] annulation reactions with activated carbon-carbon double bonds, providing rapid access to tetrahydrothiophenes.

In 2006, Pollini and co-workers exploited the reactivity of mercaptoacetaldehyde for tandem Michael–Henry or Michael–Michael reactions with electrophilic alkenes, resulting in the facile formation of 3,4-disubstituted tetrahydrothiophenes **8** using *in situ* generated nitroalkenes from the stable precursors  $\beta$ -nitroacetates **7** as the electrophilic partner of mercaptoacetaldehyde (Scheme 3).<sup>[4]</sup>



Scheme 3: Mercaptoacetaldehyde use in tandem Michael-Henry for the formation of 3,4-disubstituted tetrahydrothiophenes.

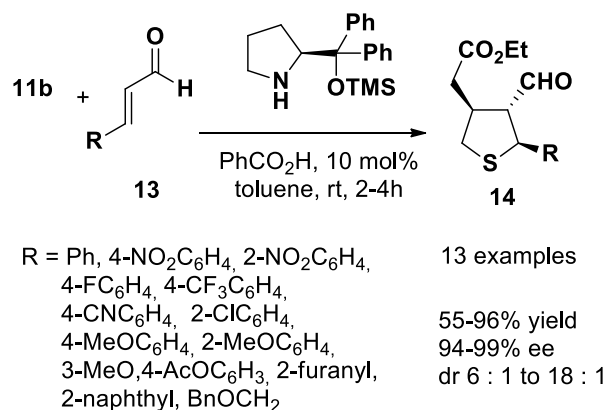
Moreover, the mild protocol developed by Bunce and Pierce for the reaction of **1** with the stabilized triphenylphosphorane **9a-c** or phosphonate **10** allowed to obtain 4-mercapto-2-butenates **11a-d**, valuable four-carbon units suitable for sulfa-Michael/aldol(Henry) type cascade reactions to produce differently substituted tetrahydrothiophenes **12** (Scheme 4).<sup>[5]</sup>



Scheme 4: Use of **1** to obtain 4-mercapto-2-butenates and subsequent use in sulfa-Michael/aldol(Henry) cascade reactions.

Since these seminal publications, the stereoselective synthesis of chiral tetrahydrothiophenes with high atom efficiency and, more importantly, good feasibility, has become a very hot topic in current research efforts.

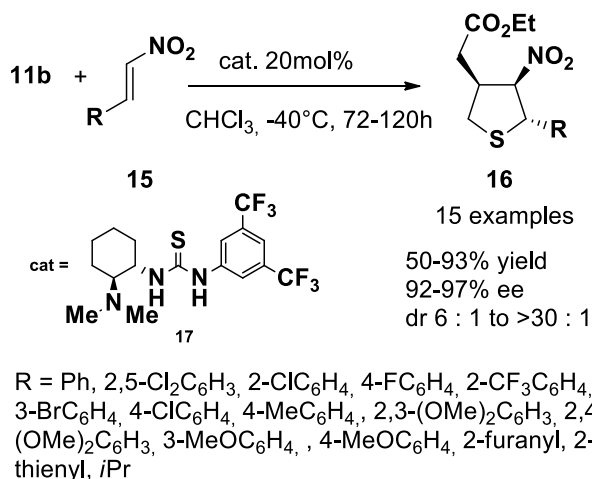
In 2007, Wang and co-workers<sup>[6]</sup> introduced the enantioselective domino thio-Michael-Michael process to furnish chiral tetrahydrothiophenes. Thus, *trans*-ethyl 4-mercapto-2-butenate **11b** has been used as reaction partner of  $\alpha,\beta$ -unsaturated aldehydes in an asymmetric organocatalytic domino Michael-Michael addition reaction in the presence of (*S*)-diphenylprolinol TMS ether. Aromatic aldehydes bearing neutral, electron-donating or electron-withdrawing groups, as well as heteroaromatic and aliphatic  $\alpha,\beta$ -unsaturated aldehydes **13** took easily part to the reaction affording chiral tetrahydrothiophenes **14** containing three stereogenic centers in good to excellent enantio- (94-99%) and diastereoselectivities (6:1 to 18:1) (Scheme 5).



Scheme 5: Preparation of chiral tetrahydrothiophenes using *trans*-ethyl 4-mercapto-2-butenate as reaction partner of  $\alpha,\beta$ -unsaturated aldehydes.

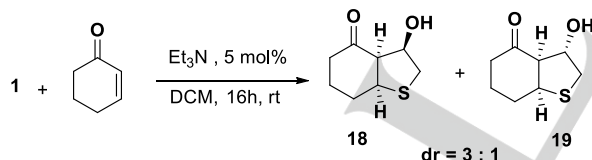
Interestingly, the same group disclosed an alternative catalytic, noncovalent activation strategy based on the use of the

bifunctional amine thiourea catalyst **17** which allowed to perform the “one-pot” thio-Michael-Michael cascade process between **11b** and nitroalkenes **15** with high enantio- and diastereoselectivity, producing trisubstituted tetrahydrothiophenes **16** possessing the nitro functional group and three different stereocentres (Scheme 6).<sup>[7]</sup>



Scheme 6: “One-pot” thio-Michael-Michael cascade process between *trans*-ethyl 4-mercapto-2-butenolate and nitroalkenes for the formation of trisubstituted tetrahydrothiophenes with high enantio- and diastereoselectivity.

In 2012, De Risi and co-workers envisioned the reaction of **1** with cyclohexenone as a straightforward route to the hexahydro-benzothiophen-4-one nucleus (Scheme 7).<sup>[8]</sup> Indeed, the sulfa-Michael/aldol reaction sequence carried out in DCM with catalytic triethylamine (5 mol %), proceeded smoothly and lead to the formation in good yield (75%) of a 3:1 mixture of the diastereomeric hexahydro-benzothiophen-4-ones **18** and **19**.

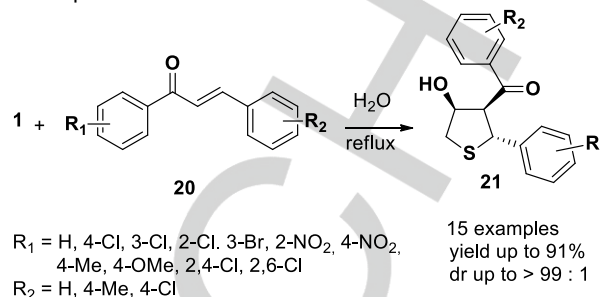


Scheme 7: Sulfa-Michael/aldol reaction of mercaptoacetaldehyde for the formation of the hexahydro-benzothiophen-4-one scaffold.

In 2014, an efficient, eco-friendly and catalyst-free construction of trisubstituted tetrahydrothiophenes has been accomplished by Song *et al.* via a sulfa-Michael/aldol (Henry) cascade reaction in water, allowing to obtain a series of tetrahydrothiophene derivatives such as **21** from a range of chalcones **20** in good yields (up to 91%) and excellent diastereoselectivities (up to >99:1) (Scheme 8).<sup>[9]</sup>

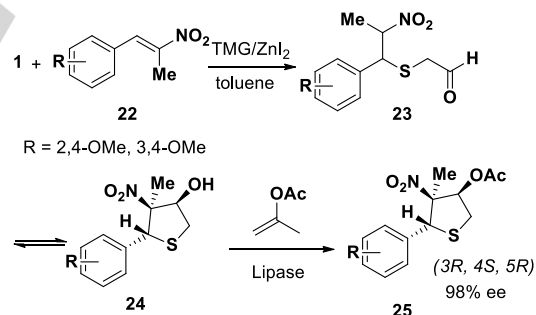
Very recently, a highly enantioselective cascade sulfa-Michael/aldol reaction catalyzed by chiral fluoride generated *in situ* from catalytic amount of KF binding with Song's oligoEG

catalyst offered a new protocol for the synthesis of trisubstituted tetrahydrothiophenes, obtained in up to 99% yield, with dr >20:1 and ee up to 98%.<sup>[10,11]</sup>



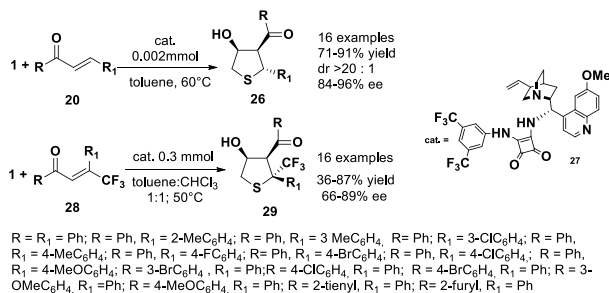
Scheme 8: Synthesis of trisubstituted tetrahydrothiophenes via a highly enantioselective cascade sulfa-Michael/aldol reaction.

Notably, Ramström and co-workers firstly described a nice example of resolution of the thiolane structures created by consecutive thia-Michael and Henry reactions using a combination of Lewis acid and base activation. Thus, the 1,1,3,3-tetramethylguanidine (TMG)/ zinc iodide-catalyzed diastereoselective sulfa-Michael/nitroaldol cascade reaction of *trans*-β-methyl-β-nitrostyrenes **22** with **1** was combined with a lipase-catalyzed kinetic resolution, one diastereoisomer of the racemic tetrahydrothiophenes **24**, present at the equilibrium together **23**, being preferentially acylated by the enzyme to give the product **25** in high ee (Scheme 9).<sup>[12][13]</sup>



Scheme 9: Diastereoselective cascade sulfa-Michael/nitroaldol reaction of *trans*-β-methyl-β-nitrostyrenes and mercaptoacetaldehyde and subsequent lipase-catalyzed kinetic resolution.

The reactivity of mercaptoaldehyde as a dual reactive substrate has been exploited by Xu and co-workers<sup>[14]</sup> as the starting move of an efficient synthesis of enantioenriched trisubstituted tetrahydrothiophenes **26** via a bifunctional amino-squaramide-catalyzed domino sulfa-Michael/aldol cascade reaction with chalcones **20** (Scheme 10).

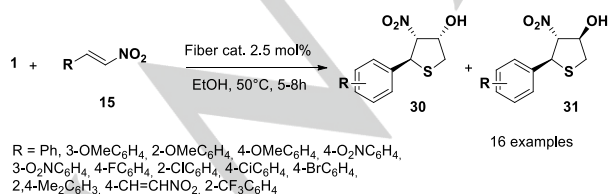


Scheme 10: Synthesis of enantioenriched trisubstituted tetrahydrothiophenes via amino-squaramide-catalyzed domino sulfaMichael/aldol reactions.

Trisubstituted tetrahydrothiophenes **26** bearing three contiguous stereogenic centers have been obtained at low catalyst loading in good to excellent yields (71–91%) and high stereoselectivities (8:1–20:1 dr and 84–97% ee) in the presence of the cinchona-derived aminosquaramide **27**, its mode of action being authoritatively discussed by Enders and coworkers.<sup>[15]</sup> A remarkable temperature effect on the reaction efficiency was observed, and a gram-scale synthesis was also successfully accomplished. The enantioinduction was not influenced by the nature and the position of the substituents on the phenyl ring of chalcones.

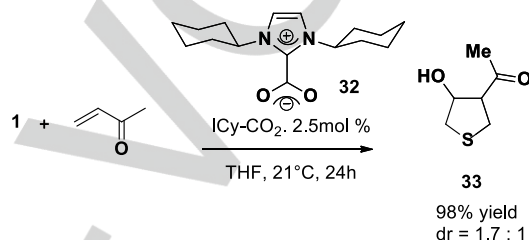
The following year, the same group applied a similar organocatalytic domino reaction to the construction of chiral CF<sub>3</sub>-containing tetrahydrothiophenes **29** by reacting **1** with β-aryl-β-trifluoromethylated enones **28** (Scheme 10).<sup>[16]</sup> The catalytic intermolecular cascade reaction has been carried out in the presence of the same cinchona alkaloid-derived squaramide catalyst **27**. The chiral trifluoromethyl tetrahydrothiophenes **29** featuring three contiguous stereocenters and a CF<sub>3</sub>-quaternary carbon center were obtained in yields of up to 87%, diastereoselectivities of up to 9:1 and enantioselectivities of up to 89%.

The easily prepared tertiary amine immobilized on fiber has been shown to act as efficient catalyst for tandem Michael-intramolecular Henry reactions between 1,4-dithiane-2,5-diol **1** and trans-β-nitrostyrenes affording the corresponding tetrahydrothiophene derivatives **30** and **31** (Scheme 11).<sup>[17]</sup> Its application to a wide range of trans-β-nitroalkenes allowed to obtain substituted tetrahydrothiophenes in good to excellent yields (75–93%) under mild conditions (with 2.5 mol % fiber catalyst at 50 °C in ethanol for 5 h). The fiber catalyst could be reused up to 10 times after simple workup procedure, with only a slight loss in catalytic activity.



Scheme 11: Catalyzed tandem Michael-intramolecular Henry reactions between mercaptoacetaldehyde and trans-β-nitrostyrenes to form tetrahydrothiophene derivatives.

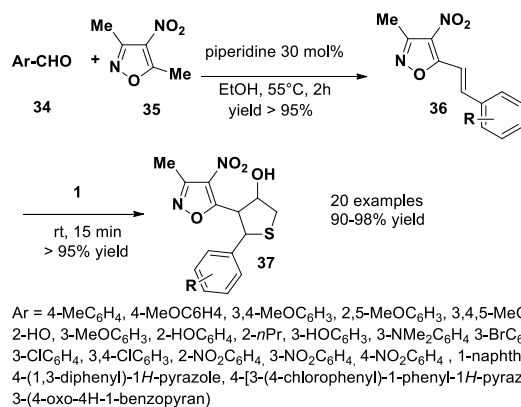
Recently, NHC-catalyzed carba-, sulfa-, and phospho-Michael additions were efficiently accomplished by Hans and co-workers using the readily available and convenient imidazol(in)ium-2-carboxylate (NHC·CO<sub>2</sub>) precatalysts (Scheme 12); however, despite the reaction of **1** with methyl vinyl ketone in the presence of ICy-CO<sub>2</sub> **32** (2.5 mol %) in THF produced the corresponding tetrahydrothiophene **33** in excellent yield, the diastereoselectivity remained modest.<sup>[18]</sup>



Scheme 12: NHC-catalyzed sulfa-Michael addition for the synthesis of tetrahydrothiophenes.

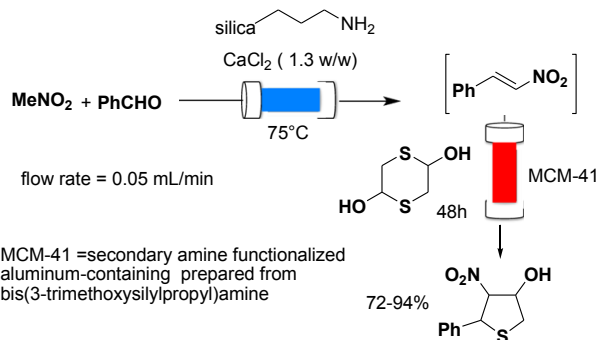
Knoevenagel condensation of various aromatic and heteroaromatic aldehydes **34** with 3,5-dimethyl-4-nitroisoxazole **35** followed by domino sulfa-1,6-Michael/intramolecular vinylogous Henry reactions between the derived nitrostyrene derivatives **36** and **1** has been elegantly designed by Kashinath et al.<sup>[19]</sup> for a rapid synthesis of highly functionalized tetrahydrothiophene (thiolane) derivatives **37** bearing the biologically useful isoxazole nucleus.

The desired products **36** could be obtained with >95% yields in 2–2.5 h overall reaction time through a careful choice of base (piperidine, 30 mol%) and solvent (ethanol). (Scheme 13).<sup>[19]</sup>



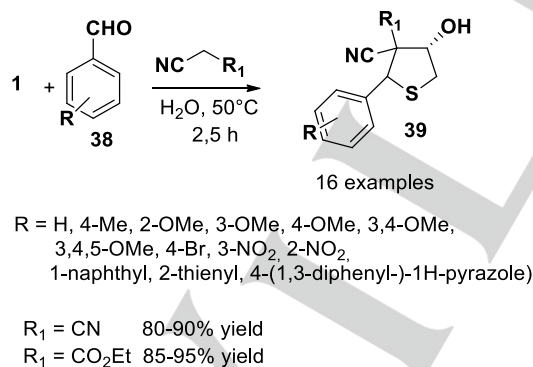
Scheme 13: Synthesis of highly functionalized isoxazole-tetrahydrothiophene hybrids.

In recent years, organic synthesis under continuous-flow conditions has attracted much attention because of its environmental friendliness, efficiency, and safety. Under this condition, the synthesis of  $\beta$ -nitrostyrene derivatives was efficiently accomplished continuously for at least 100 hours with high selectivity from aromatic aldehydes and nitromethane using readily available amino-functionalized silica gel as the catalyst. In a second step, the  $\beta$ -nitrostyrene derivatives were reacted with **1** using secondary amine-functionalized, aluminum-containing MCM-41 packed in column as the catalyst, giving rise to the formation of the desired tetrahydrothiophene in 75–94% yield during 48 h (Scheme 14).<sup>[20]</sup>



Scheme 14: Formation of trisubstituted tetrahydrothiophenes in flow conditions

Very recently, functionalized tetrahydrothiophenes **39** with quaternary centers with geminal electron withdrawing groups have been efficiently obtained in 80–95% yields by reaction of **1** with the Knoevenagel condensation products of aldehydes **38** with malononitrile or ethyl cyanoacetate in water (2 mL) at 50°C. (Scheme 15).<sup>[21]</sup>



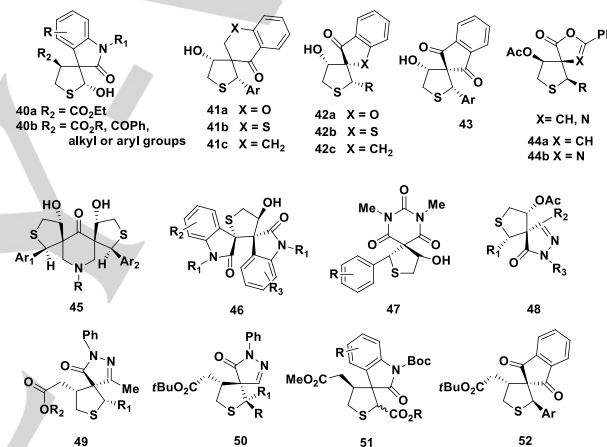
Scheme 15: Synthesis of functionalized tetrahydrothiophenes with quaternary centers with geminal electron withdrawing groups.

## 1.2 Synthesis of spirotetrahydrothiophenes

In the last years, the synthesis of spiro heterocycles has attracted a great deal of attention owing to the interesting conformational features and wide spectrum of applications

associated to this structurally unique class of molecules frequently found in many natural products and biologically active molecules. A recent review highlighted the versatility of spiro scaffolds in drug discovery owing to their inherent three-dimensionality and structural novelty.<sup>[22]</sup>

The development of methods for the stereoselective construction of chiral spirocyclic tetrahydrothiophene derivatives became a topical subject in synthetic chemistry. A variety of spirotetrahydrothiophene scaffolds anchored to different skeletons have been described in a flurry of papers that appeared in the literature in the last four years<sup>[24–39]</sup> taking advantage of the excellent anellating properties of **1** as well as the derived 4-mercapto-2-butenates **11a–d** in partnership with  $\alpha,\beta$ -unsaturated carbonyl compounds. These transformations have been very recently reviewed, highlighting the pivotal role of organocatalysis as a powerful and versatile tool for the rapid construction of spirotetrahydrothiophene motifs.<sup>[23]</sup> The main structures synthesized are listed in the following Scheme 16.



Scheme 16: Chiral spirocyclic tetrahydrothiophene derivatives.

The first synthetic approach to spirocyclic oxindole fused-tetrahydrothiophene derivatives exploiting the reactivity of **1** as anellating agent concerned the synthesis of tetrahydrothiophene-fused spirooxindoles **40a**.<sup>[24]</sup> This operation has been achieved through domino thia-Michael/aldol reaction between **1** and 3-alkenyloxindoles catalyzed by the organo-Cinchona-based squaramide **27**,<sup>[15]</sup> the reaction scope being limited to the strong electron-deficient ester group of substituted 3-alkenyloxindoles. Later, use of chiral *N,N'*-dioxide-nickel(II) complex system<sup>[25]</sup> as the catalyst allowed to extend this approach to the preparation of a broad spectrum of enantio-enriched spirocyclic oxindole-fused tetrahydrothiophene compounds **40b** (56–97% yields, 90–98% ee, 8:1 to >19:1 dr). Spirocyclic tetrahydrothiophene chromanone derivatives **41a** and **41c**, featuring three contiguous stereocenters, have been obtained in high to excellent yields (up to 99%) and with high enantioselectivities (up to 92% ee) using the readily available bifunctional squaramide organocatalyst **27** while **41b** and **41c** have been prepared with moderate to good enantioselectivities employing readily available chiral quaternary ammonium salts as

organocatalysts.<sup>[26,27]</sup> Very recently, spirocyclic tetrahydrothiophene chromanone derivatives **41c** have been enantioselectively obtained with Song's chiral oligoEG as a cation binding catalyst and catalytic amount of KF.<sup>[11]</sup> Moreover, **41a** has been conveniently obtained in a diastereoselective fashion in the presence of triethylamine.<sup>[28]</sup>

Spirocyclic tetrahydrothiophene derivative **42a**, bearing a benzofuran-3(2H)-one, has been prepared enantioselectively applying the bifunctional catalyst **27** and by using Song's chiral fluoride complex.<sup>[11,29]</sup> Replacement of the benzofuran-3(2H)-one with the benzothiophen-3(2H)-one moiety produced **42b** with moderate enantioselectivity. A library of 2'-(aryl)-4'-hydroxy-4',5'-dihydro-2'H-spiro[indene-2,3'-thiophen]-1(3H)-ones **42c** has been obtained stereoselectively through domino reactions of (*E*)-2-(aryl)-2,3-dihydro-1H-inden-1-ones and **1** in the presence of triethylamine in water.<sup>[30]</sup>

Enders and co-workers described the synthesis of tetrahydrothiophene bearing spiro indane-1,3-dione derivatives **43** in excellent yields and good stereoselectivities through a squaramide-catalyzed sulfa-Michael/aldol domino reaction,<sup>[31]</sup> while Hejmanowska and Albrecht reported the preparation spirocyclic tetrahydrothiophenes bearing either a butenolide or an azlactone moiety (**44a** and **44b**) using chiral bases derived from cinchona alkaloids as the catalyst.<sup>[32]</sup> A library of novel bis-spiropiperidone-tetrahydrothiophene hybrid heterocycles **45** has been synthesized via pseudo-three-component domino reaction of (3*E*,5*E*)-3,5-bis(arylidene)-1-methyl/benzylpiperidin-4-ones and **1** in the presence of triethylamine.<sup>[33]</sup> Chiral bis-spirooxindole tetrahydrothiophenes **46** with vicinal quaternary spirocenters has been built up through a cinchona alkaloid catalyzed enantioselective sulfa-Michael/aldol cascade reaction of isoindigos.<sup>[34]</sup>

Moreover, a green and efficient one-pot reaction of aldehydes with barbituric acid or malononitrile and **1** have been developed for the synthesis of quaternary-centered spirobarbiturate-tetrahydrothiophene hybrids **47** via Knoevenagel condensation, 1,4-thia-Michael and intramolecular aldol reactions using "on water" concept under catalyst-free conditions.<sup>[21]</sup>

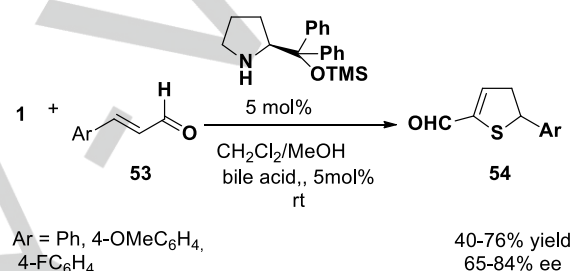
Michael/Michael reaction, one of the most powerful and reliable tools for the stereocontrolled assembly of molecular architectures, has been used as an efficient method for the construction of chiral spiro-tetrahydrothiophene derivatives. In 2016, spiro[pyrazolone-4,3'-tetrahydrothiophene] derivatives **48** and **49** have been produced in moderate to excellent yields and diastereomeric ratios (up to 98% yield and >20:1 dr) via sulfa-Michael/aldol domino reactions catalyzed by *N,N*-diisopropylethylamine in methylene chloride or 1,4-diazabicyclo[2.2.2]octane (DABCO) in toluene at 0 °C using **1** and *trans*-ethyl 4-mercapto-2-butenolate **11b** as partners of various arylidenepyrazolones.<sup>[35,36]</sup> One year later, Lattanzi and co-workers were able to obtain spirocyclic compounds **50** in good yields and fairly good diastereo- and enantioselectivities by reacting  $\alpha,\beta$ -unsaturated pyrazolones and *tert*-butyl (*E*)-4-mercapto-2-butenolate **11c** in the presence of a readily available secondary amine thiourea derived from (*R,R*)-1,2-diphenylethylenediamine.<sup>[37]</sup>

Furthermore, the reactions between *trans*-ethyl 4-mercapto-2-butenolate **11b** as the reaction partner of methyleneindolinones provided the spirooxindole-tetrahydrothiophenes **51** in high yields and excellent enantioselectivities.<sup>[38]</sup> A similar strategy has been applied to prepare chiral spiro[indane-1,3-dione-tetrahydrothiophene] skeletons **52** which have been constructed in good yields (75-99%) with high enantioselectivities (89-99% ee) and diastereoselectivities by reacting 2-arylidene-1,3-

indanediones and 4-mercapto-2-butenolate **11c** in the presence of a tertiary amine-thiourea organocatalyst.<sup>[39]</sup>

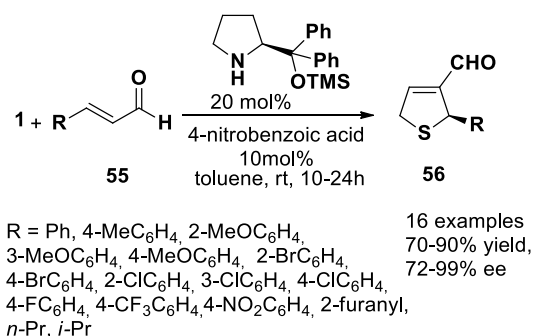
### 1.3. Synthesis of Dihydrothiophenes

Dihydrothiophenes and their derivatives are key components present in many natural products, bioactive compounds, and synthetic intermediates, and their oxidation or reduction smoothly affords thiophenes or tetrahydrothiophenes, respectively.<sup>[1,2]</sup> A stereoselective synthesis of dihydrothiophenes has been accomplished through organocatalytic asymmetric domino sulfa-Michael/aldol condensation reactions between **1** and cinnamaldehydes **53** in the presence of (*S*)-diphenylprolinol TMS ether and bile acid derivatives, giving rise to the formation of 4,5-dihydrothiophene-2-carbaldehydes **54** in moderate to good yields and enantioselectivities (Scheme 17).<sup>[40]</sup>



Scheme 17: (*S*)-diphenylprolinol TMS ether organocatalytic asymmetric domino sulfa-Michael/aldol condensation between **1** and cinnamaldehydes for the synthesis of dihydrothiophenes.

In 2010, Xu and co-workers developed an organocatalytic domino thia-Michael/aldol condensation reaction between  $\alpha,\beta$ -unsaturated aldehydes **55** and **1** catalyzed by chiral diphenylprolinol trimethylsilyl ether to produce chiral dihydrothiophenes **56** in high yields (up to 90%) and excellent enantioselectivities (up to >99% ee) (Scheme 18).<sup>[41]</sup>



Scheme 18: Organocatalytic domino thia-Michael/aldol condensation of unsaturated aldehydes with **1** to produce chiral dihydrothiophenes.

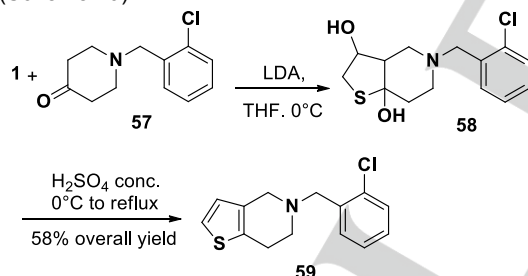
De Risi and co-workers found that the preparation of the known enantiopure (or enantioenriched) 2,5-dihydrothiophene-3

carbaldehydes **56** described by Xu and co-workers required a careful re-examination of the experimental conditions, being unable to obtain the required compounds following the reported directions.<sup>[42,43]</sup> Thus, the reaction between **1** and cinnamaldehyde was carried out in DCM instead of toluene at 40 °C for 2h, under inert atmosphere and in the presence of the commercially available chiral diphenylprolinol trimethylsilyl ether as catalyst (20 mol %) and benzoic acid (10 mol %) as additive. More recently, the catalytic versatility of pepsin has been cleverly applied to a promiscuous pepsin-catalyzed asymmetric domino thia-Michael/aldol condensation reaction of aromatic, heteroaromatic, and aliphatic  $\alpha,\beta$ -unsaturated aldehydes with **1** in buffered acetonitrile allowing to obtain the corresponding functionalized chiral dihydrothiophenes with 40–84% ee without any additive.<sup>[44]</sup>

#### 1.4. Synthesis of Thiophenes

Thiophene is a privileged five-membered heterocycle present as a subunit in numerous natural products and pharmaceuticals, and its numerous derivatives have emerged as a class of important heterocycles, which not only exhibit a variety of biological and medical properties, but are also widely used in material science and organic synthesis as versatile intermediates.<sup>[1,2]</sup>

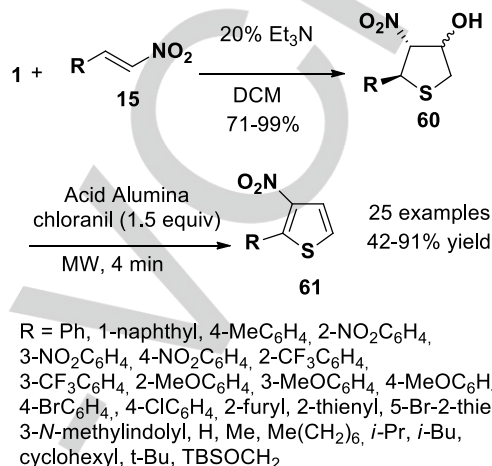
In 1991, Gooding and Beard described a short pathway to Ticlopidine **59** based on the condensation of **1** with *N*-(2-chlorobenzyl)-4-piperidone **57** in the presence of lithium diisopropylamide. Subsequent acid treatment of the fused dihydroxytetrahydrothiophene intermediate **58** promoted dehydration to the required thiophene ring system in 58% overall yield (Scheme 19).<sup>[45]</sup>



Scheme 19: Condensation of **1** with *N*-(2-chlorobenzyl)-4-piperidone and subsequent reaction for the synthesis of Ticlopidine **59**.

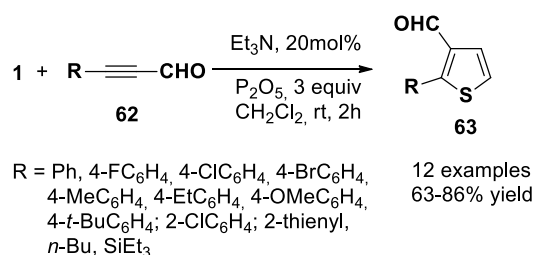
A new approach to form 3-nitro-2-substituted thiophenes **61** has been developed which involved dehydration and subsequent oxidative aromatization under microwave irradiation of the corresponding tetrahydrothiophenes **60**, obtained as a mixture of diastereoisomers in high yields by tandem conjugate-addition/nitroaldol ring closure reaction (Scheme 20).<sup>[4]</sup> A simple workup procedure removes the requirement for purification by chromatography in most cases.<sup>[46]</sup> More recently, the same research group has described a one-pot approach to the synthesis of 3-nitrothiophene and 3-nitro-2-substituted thiophenes: they optimised the dehydration and oxidation

reactions employing the tetrahydrothiophene derivatives **60**, which were obtained in 99% yield by reaction of the commercially available  $\beta$ -nitrostyrene with **1** in the presence of 25% Et<sub>3</sub>N in DCM solution.<sup>[4,47]</sup> Nonetheless, conversion to the desired thiophene has been achieved in 98% yield after heating at reflux for 24 h in the presence of silica gel (8 equiv w/w) and using DDQ (4 equiv) and molecular sieves (4 equiv w/w).



Scheme 20: One-pot approach to the synthesis of 3-nitrothiophene and 3-nitro-2-substituted thiophenes.

A triethylamine-catalyzed [3+2] cycloaddition of **1** with aromatic and aliphatic ynals **62** has been efficiently used to synthesize 3-aldehyde-2-substituted thiophenes **63** in one step and high yields (Scheme 21).<sup>[48]</sup> Triethylamine was identified as the best catalyst for this transformation, the yields decreasing to 70-80% in the presence of other organic bases such as DEA, DIPEA and pyridine. The reaction showed good tolerance for aromatic ynals, electronwithdrawing or electron donating groups in different positions of the aromatic aldehyde.



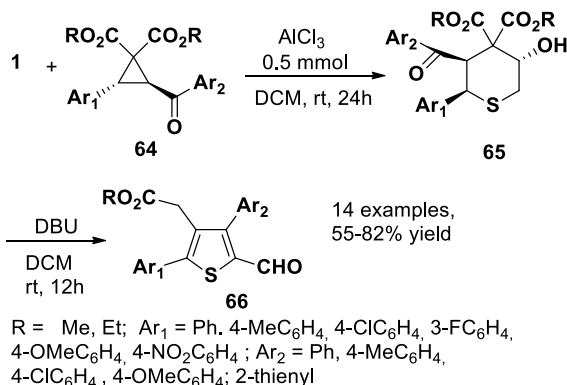
Scheme 21: Synthesis of 3-aldehyde-2-substituted thiophenes via [3+2] cycloaddition of **1** with aromatic and aliphatic ynals.

Notably, this sequence could be extended to other  $\alpha,\beta$ -unsaturated substrates, furnishing thiophene derivatives containing various functional groups such as ester and ketone groups at the 3-position of the thiophene ring.

Three examples of employment of **1** as a two-atom component in the thiophene synthesis have been reported in the literature.

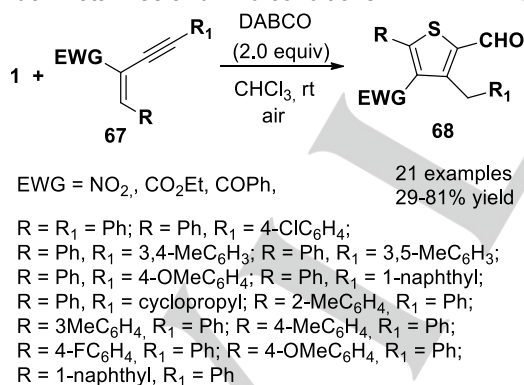


This strategy has been firstly devised by Sathishkannan and Srinivasan for the synthesis of tetrasubstituted thiophenes **66** through  $\text{AlCl}_3$ -mediated [3+3] annulation of 1,3-zwitterionic intermediates - derived from the cyclopropanes **64** - with *in situ* generated mercaptoacetaldehyde, followed by DBU-induced rearrangement of the resulting tetrahydrothiopyranols **65**, providing the target thiophenes in 55-82% yields (Scheme 22).<sup>[49,50]</sup>



Scheme 22: Employment of **1** as a two-atom component in the thiophene synthesis.

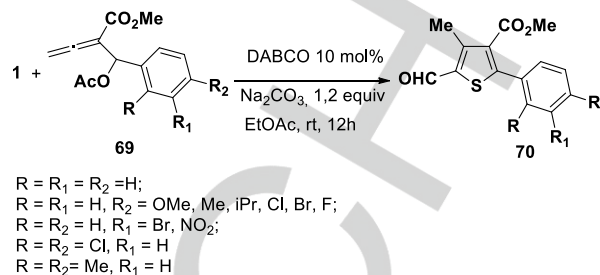
More recently (Scheme 23), the same research group described the preparation of tetrasubstituted thiophenes **68** from 1,3-enynes **67** and **1** using DABCO at room temperature, in a domino reaction sequence *via* a Michael addition, 5-exo-dig carboannulation, and oxidation under air.<sup>[51]</sup> The broad substrate scope and mild reaction conditions are significant and practical features, but the main advantages of this sequence are the direct introduction of aldehyde and nitro/keto/ester functionalities in the thiophene ring under metal-free and mild conditions.



Scheme 23: Obtainment of tetrasubstituted thiophenes from 1,3-enynes **67** and mercaptoacetaldehyde

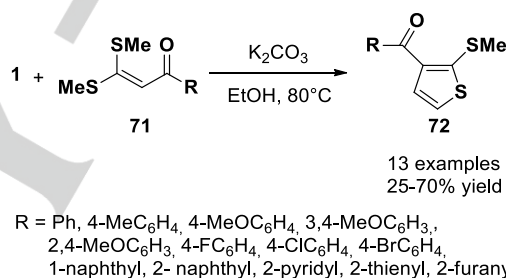
In the same year, the amine-catalyzed cascade [3+2] annulation of  $\beta$ -acetoxo allenates **69** and **1** - used here as the bisnucleophile partner - followed by oxidative

aromatization allowed to obtain fully substituted thiophene-2-carbaldehydes **70** (Scheme 24).<sup>[52]</sup>



Scheme 24: Synthesis of thiophene-2-carbaldehydes.

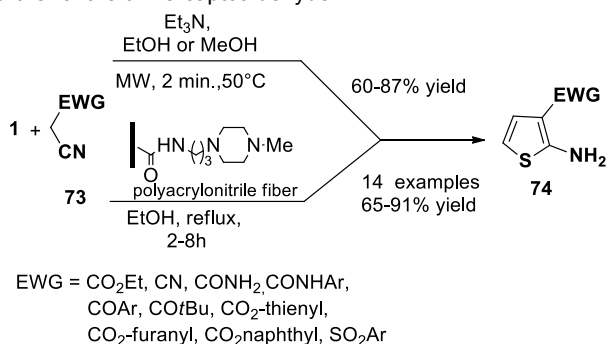
Even more recently, the reaction of  $\alpha$ -oxoketene dithioacetals **71** with **1** in the presence of anhydrous potassium carbonate in boiling ethanol has been conveniently utilized to produce the corresponding 2-(methylthio)-3-aryl/heteroaryl thiophenes **72** in 55-70% overall yields (Scheme 25).<sup>[53]</sup>



Scheme 25: Synthesis of 2-(methylthio)-3-aryl/heteroaryl thiophenes from  $\alpha$ -oxoketene dithioacetals and **1**.

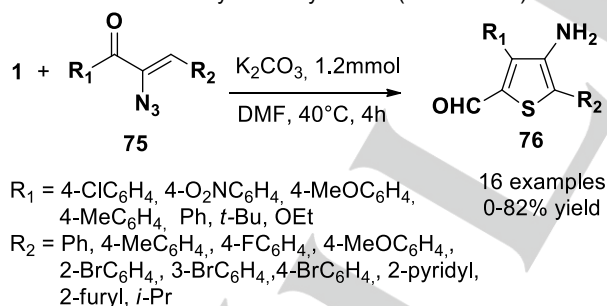
The chemistry of 2-aminothiophenes is arguably one of the most extensive and dynamic field of thiophene research,<sup>[54]</sup> the most convergent and well-established classical approach for their preparation being Gewald's reaction, a multicomponent condensation of  $\alpha$ -methylene carbonyl compound with  $\alpha$ -acetonitrile and elemental sulfur.<sup>[55]</sup> The original protocol has been widely modified since its publication by varying the reaction components and catalysts, the availability of reagents and the mild reaction conditions all contributing to the versatility of this reaction. In addition, microwave and ultrasonic irradiation have also been used to promote the Gewald reaction.<sup>[56]</sup> The air-stable, readily available **1** has been reported as convenient coupling partner as it represents a suitable substitute for both the carbonyl and sulfur partners, being the precondensation product of acetaldehyde and sulfur. Dumaitre and Dodic obtained 2-aminothiophene-3-carboxamide in 62% yield by reaction of thioacetaldehyde dimer with cyanoacetamide at 70 °C for 2 h.<sup>[57]</sup> This procedure was also used by Gutschow and Neumann in their synthesis of thieno[1,3]oxazin-4-ones as inhibitors of human leucocyte elastase.<sup>[58]</sup> In 2007, Hesse and co-workers described the expeditious synthesis of 2-

aminothiophene-3-carboxylic acid derivatives, which were obtained in two minutes under microwave irradiation and conveniently used for the synthesis of 3H-thieno[2,3-d]pyrimidin-4-one derivatives (Scheme 26).<sup>[59]</sup> A few years later, a *N*-methylpiperazine-functionalized polyacrylonitrile fiber was used to catalyze the Gewald reaction between **1** and activated nitriles **73**, affording 3-substituted-2-aminothiophenes **74** in good to excellent yields (65-91%) (Scheme 26).<sup>[60]</sup> A low catalyst loading of 8.0 mol %, simple procedure, high yields, recyclability and reusability of up to 10 times with minimal loss of catalytic activity, are all attractive features of this fiber catalyst. An extension to the Gewald reaction's scope has also allowed to obtain 3-acetyl-2-aminothiophene using cyanoacetone as partner of the  $\alpha$ -mercaptoaldehyde.<sup>[61]</sup>



Scheme 26: Gewald reaction of mercaptoacetaldehyde for the synthesis of 3-electrowithdrawing-2-aminothiophene.

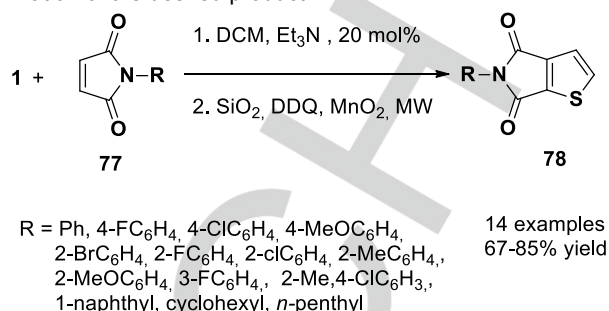
An attractive protocol has also been introduced for the preparation of 3,5-disubstituted-4-aminothiophene-2-carbaldehydes **76** by reacting vinyl azides **75** and **1**, allowing the generation of the desired products in a simple, highly efficient and eco-friendly direct synthesis (Scheme 27).<sup>[62]</sup>



Scheme 27: Preparation of 3,5-disubstituted-4-aminothiophene-2-carbaldehydes by reaction of vinyl azides and **1**.

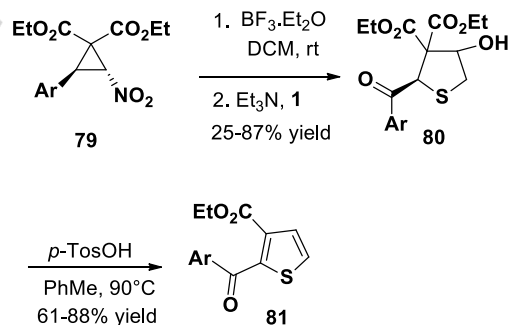
A number of 2,3-thienoimides **78** has been obtained in good to high yields through a formal [3+2] annulation reaction of **1** and *N*-substituted imides **77** through a one-pot metal-free strategy (Scheme 28).<sup>[63]</sup> A wide range of *N*-substituted imides were investigated and all reactions proceeded smoothly, providing the corresponding 2,3-thienoimides in good yields (67-85%), with the electronic nature and position of the substituents on the aryl

ring of the starting imides having no obvious influence on the formation of the desired product.



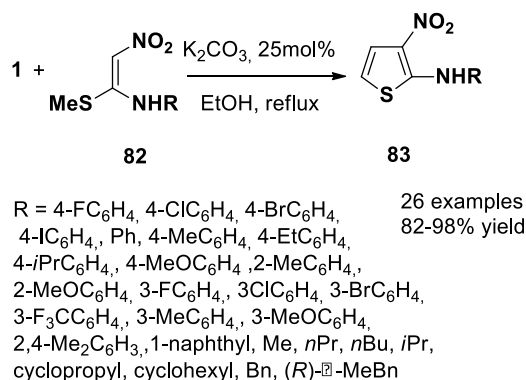
Scheme 28: Formal [3+2] annulation reaction of **1** and *N*-substituted imides for the synthesis of 2,3-thienoimides.

The reaction of *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates **79** and **1** has been conveniently utilized by Selvi and co-workers (Scheme 29).<sup>[50]</sup> to prepare 2,3-disubstituted thiophenes **81**. The two-step synthesis involved the *in situ* formation of aroylmethylidene malonates through ring-opening of nitrocyclopropane dicarboxylates **79** by action of boron trifluoride etherate followed by rearrangement and a Nef reaction. The formation of tetrahydrothiophenes **80** took subsequently place *via* tandem thiol-Michael addition/aldol reaction by addition of **1** and triethylamine to the same flask. The derived tetrahydrothiophenes **80** eventually underwent dehydration and monodecarbonylation to the required 2,3-disubstituted thiophenes **81** upon treatment with *p*-toluenesulphonic acid.



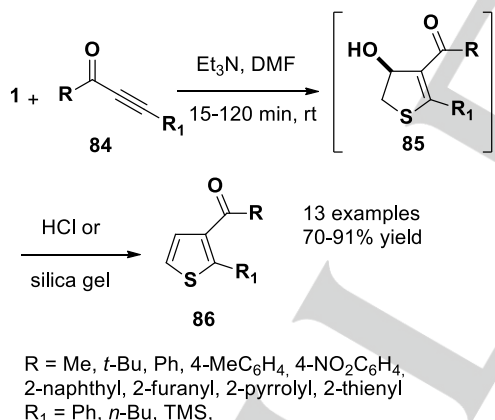
Scheme 29: Two-step synthesis of 2,3-disubstituted thiophenes from *trans*-2-aryl-3-nitrocyclopropane-1,1-dicarboxylates and **1**.

Kumar and co-workers reported the reaction of  $\alpha$ -nitroketene *N,S*-aryl/alkylaminoacetals **82** with **1** in the presence of K<sub>2</sub>CO<sub>3</sub> in refluxing ethanol as a way for the formation of 3-nitro-*N*-aryl/alkylthiophen-2-amines **83** in good yields; it is worth noting that this efficient protocol generates two carbon-carbon bonds in a single operation (Scheme 30).<sup>[64]</sup>



Scheme 30: Reaction of  $\alpha$ -nitroketene N,S-aryl/alkylaminoacetals with **1** for the formation of 3-nitro-N-aryl/alkylthiophen-2-amines.

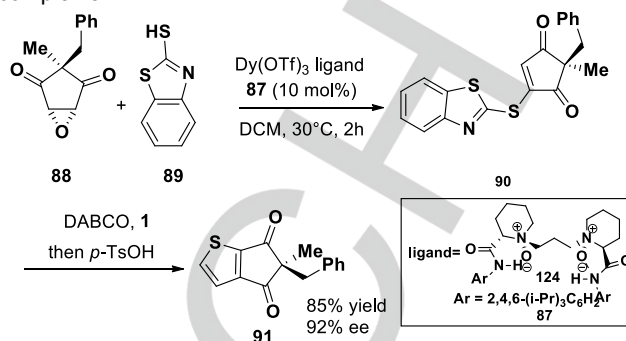
A concise and regioselective approach for the synthesis of 2,3-disubstituted thiophene derivatives **86** relied on the reaction of alkynes **84** - prepared by Sonogashira cross-coupling reaction of readily available acyl chlorides and terminal acetylene derivatives - with *in situ*-generated 2-mercaptoacetaldehyde in the presence of Et<sub>3</sub>N followed by treatment with silica gel or hydrogen chloride (Scheme 31).<sup>[65]</sup> The crude 2,3-disubstituted dihydrothiophene derivatives intermediates **85** are obtained in good to excellent yields and underwent slow dehydration upon standing in chloroform. Final chromatography using silica gel or treatment with acid completed dehydration to the desired thiophene derivatives **86**.



Scheme 31: Synthesis of 2,3-disubstituted thiophenes by reaction of alkynes and mercaptoacetaldehyde.

Recently, the optically active thiophene derivative **91** has been efficiently obtained by reaction of the (*R*)-derived desymmetrized compound **90** with mercaptoacetaldehyde in the presence of catalytic amount of DABCO, followed by the addition of 1 equivalent of *p*-TsOH (Scheme 32).<sup>[66]</sup> Compound **90** was previously obtained after the asymmetric desymmetrization of meso-epoxide **88** - derived from cyclopentene-1,3-diones - with 2-mercaptobenzothiazoles **89** through a thiolysis/elimination

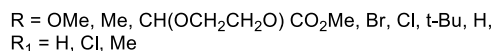
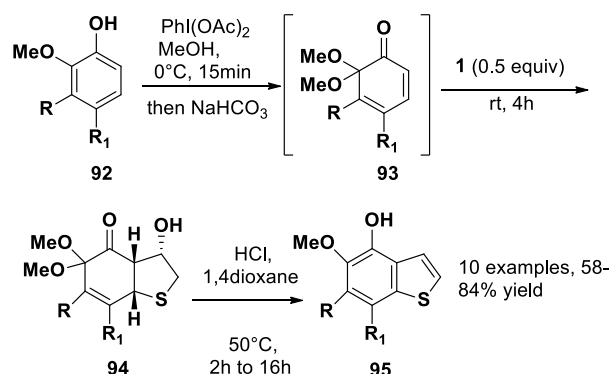
sequence in the presence of the the chiral Dy(III)/N,N'-dioxide complex **87**.



Scheme 32: Desymmetrization of meso-epoxides with 2-mercaptobenzothiazoles for the obtention of optically active thiophene derivatives.

The formation of the thiophene moiety in **91** results from a base-promoted sulfa-Michael addition/aldol/elimination reaction sequence followed by subsequent acid-promoted aromatization, in which the benzothiazole thioether group served as leaving group. Notably, this reaction could be performed in one pot, affording the thiophene derivative in 85% yield without loss in the enantiomeric excess.

Very recently, Chittimalla and Bandi developed a new synthetic method for preparing benzothiophene derivatives **95** based on tandem thia-Michael addition/intramolecular aldol reaction (a formal [3+2] annulation) between **1** and the cyclohexa-2,4-dien-1-one monoketals **93** generated *in situ* by oxidative dearomatization with methanolic PhI(OAc)<sub>2</sub> of phenols **92** to produce the corresponding tetrahydrobenzothiophenone derivatives **94**, further converted to benzothiophenes by treatment with 4N HCl at 50 °C (Scheme 33).<sup>[67]</sup>



Scheme 33: Synthesis of benzothiophene derivatives via formal [3+2] annulation between **1** and cyclohexa-2,4-dien-1-one monoketals.

## 2. Synthesis of 1,3-oxathiolane

An efficient access to the chiral 1,3-oxathiolane motif was required to prepare bulk quantities of Lamivudine **96** and analogues **97-99** depicted in Figure 1.

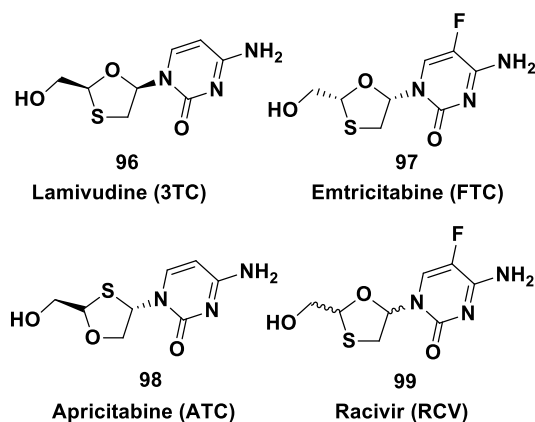
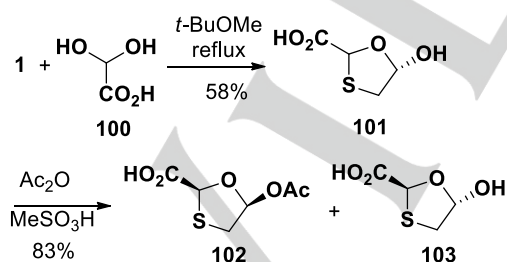


Figure 1: Lamivudine **96** and analogues **97-99**.

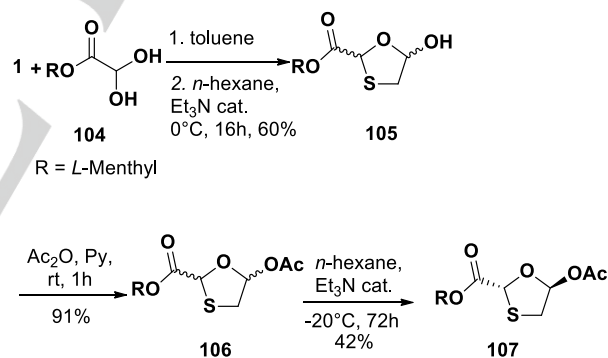
Despite their structural simplicity, these compounds have represented a major synthetic challenge because of the need for a chemistry enabling stereochemical control of two potentially epimerizable stereocenters on the sulfur-containing heterocycle. In 1995, a Glaxo research group described the synthesis of the chiral oxathiolane, the opening move being the reaction of glyoxylic acid monohydrate **100** and **1** in refluxing *tert*-butyl methyl ether under azeotropic conditions to give the *trans* hydroxy acid **101** in 58% yield.<sup>[68]</sup> Its treatment with acetic anhydride in the presence of a catalytic amount of methanesulfonic acid provided a 1:2 mixture of the *cis*- and *trans*-acetoxo acid **102** and **103**, with a combined yield of 83%. The *trans* isomer **103** was isolated in form of white crystals from the mixture by fractional crystallization from benzene (22% based on a single isomer). After extensive efforts, the resolution of this compound has been achieved readily *via* its menthyl ester derivatives (Scheme 34).



Scheme 34: reaction of glyoxylic acid monohydrate and **1** for access to the chiral 1,3-oxathiolane motif.

Ten years later, Whitehead and co-workers described a very efficient synthetic route for the partial enantioselective synthesis of lamivudine **96** - also known as 3TC - the key

step being a highly effective dynamic resolution of the 5-hydroxyoxathiolane, followed by chlorination and introduction of the cytosine residue.<sup>[69]</sup> Initially, the 5-hydroxyoxathiolane was prepared by heating a mixture of menthyl glyoxylate hydrate **104** with 1,4-dithiane-2,5-diol in toluene. This procedure produced a mixture of four diastereoisomers **105** as a 35:35:15:15 ratio. Crystallization from *n*-hexane gave the desired diastereoisomer in 34% yield, corresponding to approximately all of the desired isomer in solution. To increase the yield of the desired diastereoisomer it was found that the rapid equilibration at C-5 occurred in dichloromethane or chloroform, giving a mixture of  $\beta$  and  $\alpha$  isomers, but no isomerisation at C-2 was observed. Access to enantiopure 5-acetoxo-oxathiolane **107** (2*R*,5*R*) was explored by coupling reaction between commercially available *L*-menthyl glyoxylate monohydrate **104** and **1**, followed by treatment of the crude mixture with a Et<sub>3</sub>N-containing *n*-hexane solution, and this was found to provide hemiacetal **105** (60% yield). After acetylation to **106**, subsequent addition of *n*-hexane/Et<sub>3</sub>N is claimed to enable both the rapid interconversion among the stereoisomers and the selective precipitation of the sole (2*R*,5*R*)-stereoisomer **107** (Scheme 35). Recently, Palumbo and co-workers identified, in contrast with the aforementioned Whitehead's findings, two major acetate stereoisomers **106** having the C2 and C5 stereocenters in a *trans* relationship of hemiacetals.<sup>[70]</sup>

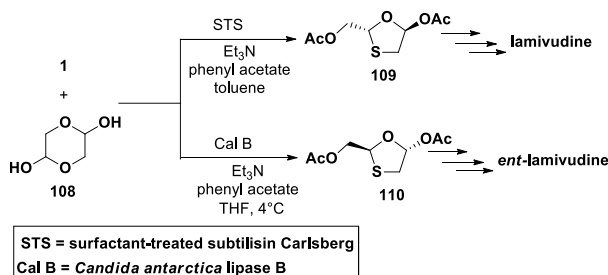


Scheme 35: Recent synthetic route for the partial enantioselective synthesis of lamivudine **96**.

In 2017, Mandala and co-workers were able to transfer the results of their improved batch synthesis of lamivudine **96** into continuous flow synthesis, the key intermediate **107** being prepared by an integrated two-step continuous flow process from *L*-menthyl glyoxalate hydrate **104** and **1** in a single solvent and 95% overall conversion.<sup>[71,72]</sup>

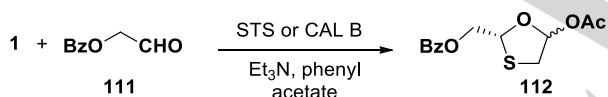
By taking advantage of the dynamic formation of hemithioacetals, an efficient, three-step synthesis of lamivudine through a surfactant-treated subtilisin Carlsberg (STS)-catalyzed dynamic kinetic resolution (DKR) protocol has been described by Ramström and co-workers (Scheme 36).<sup>[73]</sup> Thus, the key enantioenriched 1,3-oxathiolane intermediate **109** for lamivudine was obtained by mixing **1**

and **108** in toluene in the presence of triethylamine as the base and phenyl acetate as acyl donor; furthermore, the enantiomer of lamivudine **110** was also accessible when STS was replaced by *Candida antarctica* lipase B (CAL B) (Scheme 36), thus representing a flexible stereocontrol in the asymmetric formation of five-membered oxathiolane derivatives.



Scheme 36: Dynamic kinetic resolution of 1,3-oxathiolane from **1**.

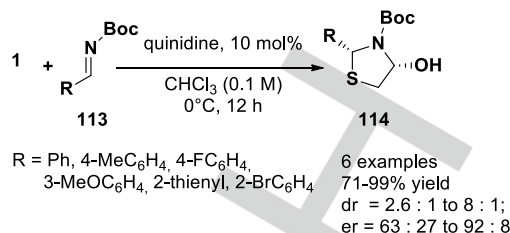
The great importance of the hemiacetal hydroxyl group is evidenced from the synthesis of the intermediate **112** using benzoyloxyacetaldehyde **111** where high ee were obtained with both CAL B and STS (Scheme 37). The origin of enantioenrichment in enzyme-catalyzed dynamic kinetic resolution of 1,3-oxathiolane derivatives, key intermediates for asymmetric lamivudine synthesis, was elucidated by the same group: the chirality control was determined by chiral HPLC and NOE NMR spectroscopy using a modified 1,3-oxathiolane compound obtained through enzyme-catalyzed selective hydrolysis. Solvent-dependent stereoselectivity was observed under biphasic conditions using different organic solvents with phosphate buffer.<sup>[74]</sup>



Scheme 37: Formation of 1,3-oxathiolane from **1**.

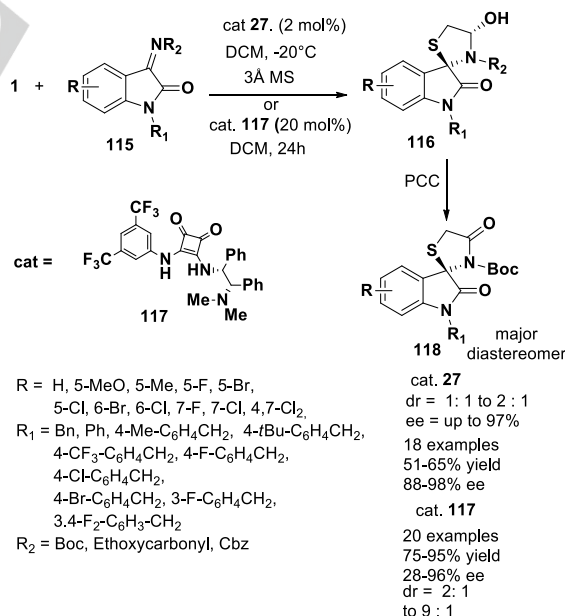
### 3. Synthesis of 1,3-thiazoles and thiazolidines

An organocatalytic enantio- and diastereoselective formal [3+2] annulation between imines **113** and **1** opened a rapid route to chiral thiazolidine-based molecules **114** starting from a readily available catalyst and achiral starting materials (Scheme 38).<sup>[75]</sup> Thus, quinidine has been efficiently used to catalyze the enantio- and diastereoselective formal [3+2] annulation of imines **113** and 2-mercaptoacetaldehyde to assemble substitute thiazolidines **114**. This bifunctional catalyst is able to activate both reaction partners, the sulfur addition to the imine being controlled by the chiral backbone. The subsequent cyclization occurred through addition of the nitrogen atom to the aldehyde group leading to the formation of the desired product.



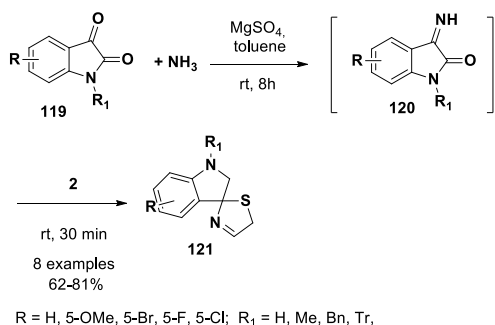
Scheme 38: Quinidine-catalyzed enantio- and diastereoselective formal [3+2] annulation of imines and 2-mercaptoacetaldehyde **2** for the assembly of substituted thiazolidines.

In 2016, two groups described the asymmetric formal [3+2] annulation of **1** to isatin-derived ketimines **115** as a facile and efficient method for the construction of chiral spirooxindole-4-thiazolidines **116** using chiral squaramide catalysts **27** and **117** (Scheme 39). In the first case, the [3+2] annulation proceeded smoothly at  $-20^{\circ}\text{C}$  producing the major diastereomer **116** with 2:1 dr and 97% ee after 12 hours.<sup>[76]</sup> These compounds were readily converted into the corresponding spirooxindole-4-thiazolidinones **118** without loss of the enantioselectivity by simple oxidation, and have been successfully applied to the synthesis of a novel class of *Mycobacterium tuberculosis* inhibitors. Alternatively, spirocyclic 3-aminooxindoles were also obtained in very good yields (up to 95%), with moderate to good diastereoselectivities (up to 9:1 dr) and very good enantioselectivities (up to 97% ee) through the same reaction in the presence of the chiral tertiary amine-squaramide catalyst **117**.<sup>[77]</sup>



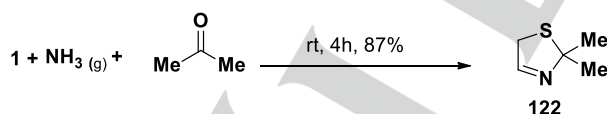
Scheme 39: Asymmetric formal [3+2] annulation of **1** to isatin-derived ketimines for the synthesis of spirooxindole-4-thiazolidinones.

Very recently, Silvani and coworkers described a one-pot, three-component reaction employed for the successful synthesis of biologically relevant, highly functionalized spirooxindole-fused 3-thiazoline derivatives **121** (Scheme 40).<sup>[78]</sup> Thus, application of an Asinger-type reaction to a series of substituted isatins **119** as the oxo component, ammonia and 2-mercaptoacetaldehyde **2** allowed to obtain efficiently a number of spirooxindole-fused 3-thiazoline derivatives **121** through the intermediates **120**.<sup>[79–81]</sup> The desired thiazolines were obtained with yields up to 81% for the most reactive *N*-Me isatin through a simple and rapid protocol.



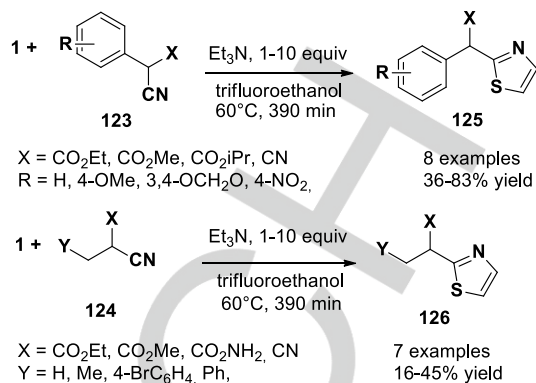
Scheme 40: Asinger-type reaction to substituted isatins, ammonia and 2-mercaptoacetaldehyde **2** for the obtention of spirooxindole-fused 3-thiazoline derivatives.

In 2016, Dömling and co-workers described a concise approach to the synthesis of all 20 common natural proteinogenic and four other  $\alpha$ -amino acid-isosteric  $\alpha$ -amino tetrazoles.<sup>[82]</sup> The synthesis of cysteine analogue could not be obtained using mercaptoacetaldehyde dimer, the desired Ugi product being not formed; therefore, a different strategy was devised involving the use of 2,2-dimethylthiazolidine **122**, a bench-stable liquid, well known to work as a Ugi-ready protected form of mercaptoacetaldehyde component in the classical Ugi-4 Component Reaction (CR). In the end, the target cysteine analogue was readily synthesized in good yields in one pot by another multi-component reaction, the Asinger-3CR of acetone, ammonia and mercaptoacetaldehyde dimer **1** (Scheme 41).



Scheme 41: Asinger-3CR of acetone, ammonia and mercaptoacetaldehyde dimer **1**.

As above described,<sup>[55–59]</sup> **1** could be used as the aldehyde precursor in a modified Gewald reaction starting from nitriles to give 2-substituted aminothiophenes.

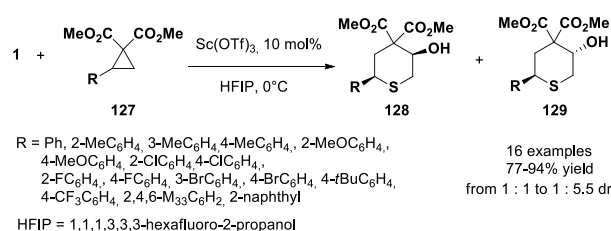


Scheme 42: Gewald-type reaction for the formation of the 2-aminothiophenes from 1,4-dithiane-2,5-diol **1** and appropriately substituted  $\alpha$ -methine nitrile.

In fact, Baxendale and co-workers demonstrated that the substitution by an alkyl or aryl group adjacent to the cyano group of the nitrile precursor predetermines the reaction outcome by blocking the Gewald-type mechanism responsible for the formation of the 2-aminothiophenes leading to the exclusive formation of 2-substituted thiazoles **125** and **126** from readily available, air stable 1,4-dithiane-2,5-diol **1** as precursor for 2-mercaptoacetaldehyde, and the appropriately substituted  $\alpha$ -methine nitrile **123** and **124** (Scheme 42).<sup>[83]</sup>

#### 4. Synthesis of tetrahydropyransols

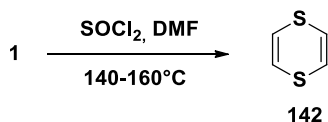
Catalytic [3 + 3] annulation of **1** and activated cyclopropanes has been employed as an efficient reaction for the synthesis of thiazines and oxathianes. The cycloaddition reactions of donor-acceptor cyclopropanes represent powerful tools for the construction of various carbocycles and heterocycles and have been intensively studied in recent decades.<sup>[50]</sup> Srinivasan and co-workers described the one-pot method for the synthesis of tetrasubstituted thiophenes **66** from tetrahydrothiopyranols **65**, in turn obtained from the [3+3] annulation of *trans*-2-aryl-3-arylcyclopropane-1,1-dicarboxylates **64** with **1** in the presence of stoichiometric amounts of  $\text{AlCl}_3$  (Scheme 22).<sup>[49]</sup> Interestingly, the  $\text{Sc}(\text{OTf})_3$ -catalysed [3+3] annulation of cyclopropane 1,1-diester **127** with **1** under mild reaction conditions allowed to obtain the synthesis of polyfunctionalized tetrahydrothiopyran derivatives **128** and **129** via a ring-opening/aldol cascade reaction (Scheme 43).<sup>[84]</sup>





The ability of compounds **141** to bind to gold surfaces was assessed by a number of techniques, such as cyclic voltammetry, electrochemical impedance spectroscopy ToF-SIMS, and XPS, and it was found that these novel bicyclic sulfides interact favourably with gold surfaces, with minimal fragmentation. However, the adsorption and film packing properties were greatly compromised by an *N*-pyridyl substitution. The findings then indicate that the surface behaviour of *N*-substituted 2,5-dithia-7-azabicyclo[2.2.1]heptanes varies with respect to the *N*-substitution and the nature of the substituent, suggesting that the adsorption profiles and the film packing of bicyclic sulfides on gold surfaces are highly dependent on the binding interface and the molecular orientation.

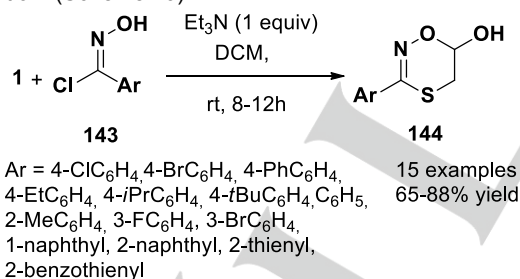
Excellent yields of 1,4-dithiin **142** were obtained by heating a dry DMF solution of **1** and 2.5 equivalents of thionyl chloride to reflux (Scheme 48).<sup>[89]</sup>



Scheme 48: Synthesis of 1,4-dithiin **142**.

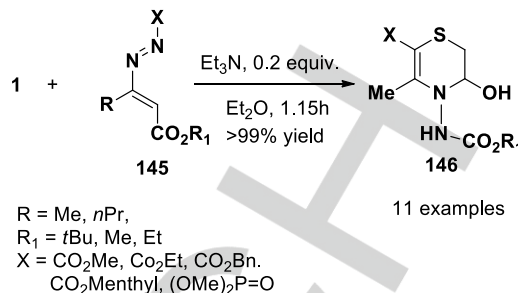
A particular attention has been recently devoted to 1,4-dithiins owing to their unique electronic and conducting properties as well as their use for the preparation of different sulfur heterocycles.<sup>[90]</sup>

Perumal and co-workers described a facile and efficient synthesis of novel 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols **144** presumably involving the concomitant *in situ* generation in the presence of triethylamine of both 2-mercaptoacetaldehyde **2** and (*E*)-*N*-hydroxyarylimidoyl chlorides **143** for the required [3+3] annulation. (Scheme 49).<sup>[91]</sup>



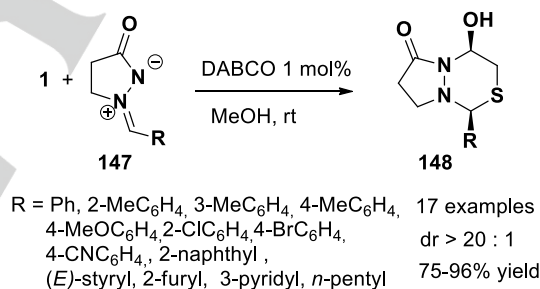
Scheme 49: Synthesis of novel 3-aryl-5,6-dihydro-1,4,2-oxathiazin-6-ols from the reaction of (*E*)-*N*-hydroxyarylimidoyl chlorides and **1** in the presence of triethylamine.

Recently, a one-pot base-catalysed strategy for an approach to 1,4-thiazines **146** obtained in total atom economy and in quantitative yields was based on sulfa-Michael addition/formal [3+3] annulation cascade reaction between **1** and 1,2-diaza-1,3-dienes **145**, as reported by Attanasi and coworkers (Scheme 50).<sup>[92]</sup>



Scheme 50: Synthesis of 1,4-thiazines **146** via sulfa-Michael addition/formal [3+3] annulation cascade reaction between **1** and 1,2-diaza-1,3-dienes.

An unusual diastereoselective [3+3] cycloaddition of **1** with azomethine imines **147** catalyzed by DABCO.<sup>[93]</sup> has been proposed as a useful way to prepare a variety of highly functionalized six-membered dinitrogen-fused sulfur-containing heterocycles **148** in good to high yields (75-96%) with excellent diastereoselectivities (>20:1 dr). (Scheme 51). Azomethine imines bearing electron-rich and electron-deficient groups at different positions on the aromatic ring could be efficiently used allowing to obtain very interesting heterocyclic products through a synthetically practical methodology also applicable in a gram-scale with a simple workup.

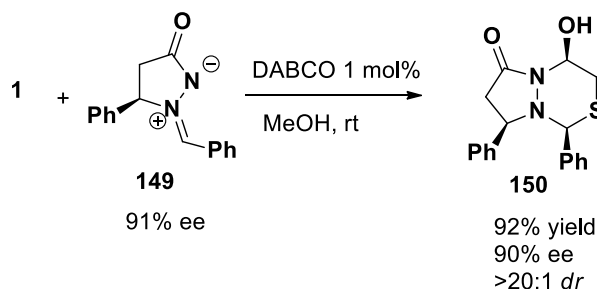


Scheme 51: Diastereoselective [3+3] cycloaddition of **1** with azomethine imines **147** for the synthesis of highly functionalized six-membered dinitrogen-fused heterocycles,

This reaction has been theoretically studied using DFT computational calculations to gain insights of the mechanisms and to explain the observed diastereoselectivity. A plausible catalytic cycle has been proposed, the tertiary amine of the catalyst providing suitable basicity to enhance the nucleophilicity of mercaptoacetaldehyde generated from **1** under equilibrium conditions.<sup>[94]</sup>

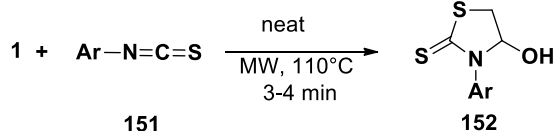
Later, the kinetic resolution of the azomethine imines has been successfully obtained with high selectivity factors (*S* factor up to 67). The base-catalyzed [3+3] annulation of the resolved enantioenriched azomethine imine **R-149** (R = Ph, 91% ee) with **1** in the presence of 1 mol% of DABCO proceeded smoothly in 20 min to produce the highly functionalized sulfur-containing heterocycle **150** in 92% yield with exclusive diastereoselectivity and maintained enantioselectivity (Scheme 52).<sup>[95]</sup>





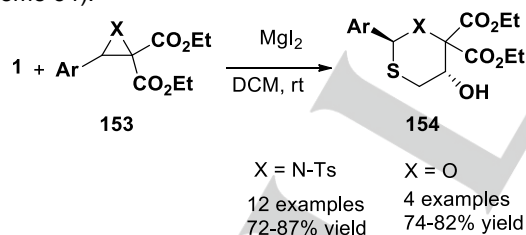
Scheme 52: Base-catalyzed [3+3] annulation of resolved enantioenriched azomethine imine **R-149** with **1** for the synthesis of highly functionalized sulfur-containing heterocycle **150**.

A domino reaction of aryl isothiocyanates **151** and **1** under solvent- and catalyst-free microwave irradiation paved the way for a highly atom efficient synthesis of 4-hydroxy-3-arylthiazolidine-2-thiones **152**. (Scheme 53).<sup>[96]</sup> This sequence could be also applied to aryl isocyanates to afford 3-phenylthiazol-2(3*H*)-ones in good yields.



Scheme 53: Synthesis of 4-hydroxy-3-arylthiazolidine-2-thiones **152** through novel domino reactions of aryl isothiocyanates **151** and **1** under solvent- and catalyst-free microwave irradiation.

In 2017, functionalized thiazine and oxathiane derivatives **154** have been efficiently built up through Lewis acid catalyzed [3 + 3] annulation of *N*-tosylaziridine dicarboxylates and oxiranes **153** with *in situ* generated mercaptoaldehyde.<sup>[97]</sup> (Scheme 54).



Scheme 54: Lewis acid-catalyzed [3 + 3] annulation of *N*-tosylaziridine dicarboxylates and oxiranes **153** with *in situ* generated mercaptoaldehyde **2** for the synthesis of functionalized thiazine and oxathiane derivatives.

## 6. Conclusions

The long journey of 1,4-dithiane-2,5-diol around the synthesis of sulfurated heterocycles is far to be concluded. This overview summarized the applications of a versatile and inexpensive starting material for the synthesis of a variety of sulfur containing heterocycles. It is relevant to underline the

ability of 2-mercaptoacetaldehyde to function as a useful platform molecule for the synthesis of important heterocycles, including thiophene and 1,3-thiazole families and, more generally, for development of new, organocatalytic asymmetric reactions.

Moreover, the use of **1** as a C2 synthon for the construction of nitrogen-containing heterocycles rather than sulfur-containing heterocycles via desulfurization has been recently described by Wu's group: the synthesis of 2-acylquinolines from methyl ketones and arylamines using 1,4-dithane-2,5-diol as an ethylene surrogate represents a further demonstration of its versatility in heterocyclic chemistry.<sup>[98]</sup>

**Keywords:** 1,4-Dithiane-2,5-diol; Heterocycles; Thiophene; Michael/Aldol reactions.

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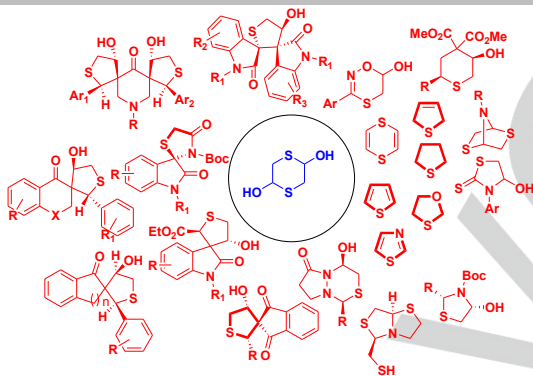
## Entry for the Table of Contents (Please choose one layout)

Layout 1:

## MICROREVIEW

Text for Table of Contents:

This microreview highlights the utility of 1,4-dithiane-2,5-diol as the cheap and commercially available starting material for use in organic and medicinal chemistry synthesis.

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Title 1,4-Dithiane-2,5-diol: An Attractive Platform for the Synthesis of Sulfur Containing Functionalized Heterocycles