Overview of the Chemistry of 2-Thiazolines

Annie-Claude Gaumont,* Mihaela Gulea,* and Jocelyne Levillain

Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, INC3M, FR 3038, ENSICAEN & Université de Caen, 14050 Caen, France

Received February 26, 2008

Contents

1. Introduction 1371
2. Syntheses of 2-Thiazolines 1371
   2.1. From β-Amino Thiols 1372
      2.1.1. With Nitriles 1372
      2.1.2. With Carboxylic Acids and Esters 1373
      2.1.3. With Iminoethers 1374
      2.1.4. With *N*-Acylbenzotriazoles 1374
      2.1.5. With Iminium Triflates 1374
      2.1.6. With α,α-Difluoroalkylamines 1374
      2.1.7. With Aryl Ketonitriles 1374
      2.1.8. By Ru-Catalyzed Oxidation of Thiazolidines 1374
      2.1.9. From S-Protected Amino Thiols 1374
   2.2. From β-Amino Alcohols 1375
      2.2.1. Using Sulfurating Agents 1375
      2.2.2. Using Thioacylating Agents 1378
   2.3. Miscellaneous 1380
3. Reactivity and Synthetic Applications of 2-Thiazolines 1381
   3.1. Synthesis of Aldehydes and Ketones 1382
   3.2. Synthesis of Thiazoles 1383
   3.3. Synthesis of β-Amino Thiols 1384
   3.4. Synthesis and Applications of α,β-Unsaturated Thiazolines 1385
   3.5. Synthesis of Thiazolinium Salts 1385
   3.6. Miscellaneous 1387
      3.6.1. Reactions with C=N Electrophiles 1387
      3.6.2. Ketene−Imine Cycloadditions 1387
      3.6.3. Reactions in the Ortho Position of 2-Aryl-Thiazolines 1387
      3.6.4. Reactions Involving Functional Groups on the Thiazoline Ring 1388
4. Thiazoline Compounds of Biological Importance 1388
   4.1. Natural Products 1388
      4.1.1. Thiazoline-Containing Polyazoles 1388
      4.1.2. Thiazoline-Containing Linear Peptides 1389
      4.1.3. Thiazoline-Containing Cyclopeptides 1390
      4.1.4. Hydroxy Aromatic and Heteroaromatic Thiazolines 1391
      4.1.5. Other Structures 1391
      4.1.6. Thiazoline-Containing Aroma and Flavors 1391
   4.2. Synthetic Products 1392
5. Chiral 2-Thiazolines as Ligands for Asymmetric Catalysis 1392
   5.1. Hydrosilylation 1393
   5.2. Allylic Substitution 1394
   5.3. Diels−Alder Reaction 1397
   5.4. Cyclopropanation 1397
   5.5. Henry Reaction 1397
   5.6. C−P Bond Formation 1398
   5.7. Addition of Nitroalkanes to Nitroalkenes 1398
   5.8. Friedel−Crafts Alkylation 1398
6. Conclusion 1398
7. Acknowledgments 1399
8. References 1399

* To whom correspondence should be addressed. Phone: 33-231452873/33-231452898. Fax: 33-231452877. E-mail: annie-claude.gaumont@ensicaen.fr, mihaela.gulea@ensicaen.fr.

1. Introduction

Heterocyclic compounds are of outstanding importance as pharmaceuticals, agrochemicals, fine and bulk chemicals, and ligands for catalysis.[1] Among the different heterocycles, 2-oxazolines have been widely studied and reviewed,[2] especially chiral oxazolines[3] and bis(oxazolines),[4] due to their wide application as ligands for asymmetric catalysis. Compared to 2-oxazolines, the sulfur analogues, that is, the 2-thiazolines, have received less attention. To the best of our knowledge, there is only one review, published by Fustero et al. in 2001,[5] which focuses on the preparation and to some extent synthetic applications of both 2-alkyl-2-thiazolines and 2-alkyl-2-oxazolines. Recently, various groups have paid attention to the chemical properties of 2-thiazolines, mainly because of the unique properties of sulfur. In different reports, a reactivity that often dramatically differs from that of the corresponding oxazoline derivatives was pointed out.

In this contribution, we wish to give an overview of the chemistry of 2-thiazolines, including new methodologies for their preparation, and recent applications, such as their growing use in organic synthesis in the biological field and asymmetric catalysis as ligands. The methods enabling access to thiazolines will first be underlined. Then the reactivity and applications in the fields of organic synthesis, biomolecules (natural or not), and catalysis will be documented. The structure of the thiazolines treated in this review is illustrated in Figure 1. Compounds bearing atoms other than carbon at the 2-position, including 2-*H*-thiazolines, 2-aminothiazolines, or 2-halogenothiazolines, are beyond the scope of this review. Cited references are restricted to journals, reviews, and books. Literature coverage for this review extends up to September 2007.

2. Syntheses of 2-Thiazolines

2-Thiazoline derivatives are prepared from either β-amino thiols or β-amino alcohols (Scheme 1). In the first case, the sulfur atom arises from the amino thiols. With the amino alcohols the sulfur comes from either a sulfurating agent or

10.1021/cr800189z CCC: $71.50
Published on Web 01/20/2009

Annie-Claude Gaumont was born in 1964 in Vannes (Morbihan, France). She studied chemistry at the University of Rennes (France). In 1991 she joined the research group of Dr. J.M. Denis, graduating with her Ph.D. degree. She had postdoctoral experience as a research associate with Professor J. M. Brown at the University of Oxford (U.K.). She returned to the University of Rennes as a CNRS researcher and in 2001 moved to Caen (Normandy), where she was promoted Professor of Organic Chemistry. Her group research interests mainly focus on phosphorus and sulfur chemistry in catalysis (ligands) and synthesis (preparation of new building blocks) and development of new media for catalysis (Ionic Liquids, supported phases such as SILP).

Mihaela Gulea was born in 1967 in Romania. She graduated from "Facultatea de Chimie Industriala" of Bucharest in 1990. She then moved to France and in 1997 received her Ph.D. degree from the University of Rouen under the supervision of Professor N. Collignon. After a postdoctoral stay in the group of Professor M. Malacria (Paris), in 1999 she obtained a permanent position at the "Centre National de la Recherche Scientifique" (CNRS) in the group of Dr. S. Masson in Caen. Then she joined the group of Professor A.-C. Gaumont in 2004. Her research interests focus on the synthesis and reactivity of organophosphorus and organosulfur compounds.

a thiocarbonyl-containing reagent. Miscellaneous methods are also reported in section 2.3. We hope that this classification will offer chemists an easy guide to the preparation of 2-thiazolines.

2.1. From β-Amino Thiols

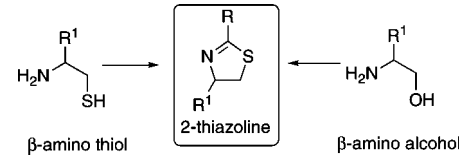
Condensation of β-amino thiols with nitriles or carboxylic acid derivatives is a straightforward route to 2-thiazolines (Scheme 2). However, difficult access to a large variety of β-amino thiols, especially in enantiopure form, is a severe limitation of this method. Moreover, only two 2-amino thiols, one achiral (cysteamine) and one enantiopure (L-cysteine), are widely commercialized.

Jocelyne Levillain was born in Saint-Lô (France) in 1963. She studied chemistry at the University of Caen and in 1994 completed her Ph.D thesis under the supervision of Dr. M. Vazeux. After a postdoctoral stage at the Royal College of Surgeon in Ireland with Professors K. Nolan and D. Fitzgerald, she returned to Caen at the University as "Maitre de Conférences" in J. L. Ripoll's group, working on flash vacuum thermolysis. In 2001 she joined the group of Professor A.-C. Gaumont, and she is now involved in the chemistry of chiral ionic liquid.

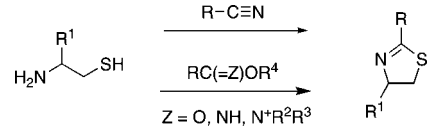
R = alkyl, alkenyl, aryl, carbonyl...

Figure 1. General structure and numbering of the thiazoline heterocycle.

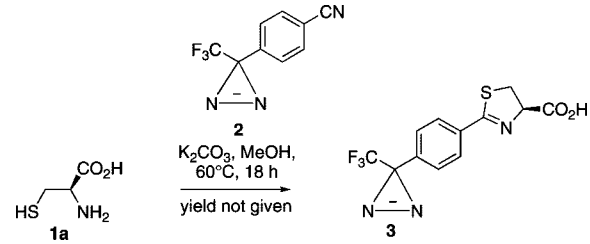
Scheme 1. General Preparation of 2-Thiazolines from β-Amino Thiols or β-Amino Alcohols



Scheme 2. General Preparation of 2-Thiazolines from β-Amino Thiols



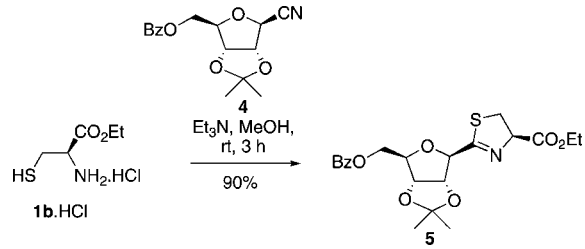
Scheme 3



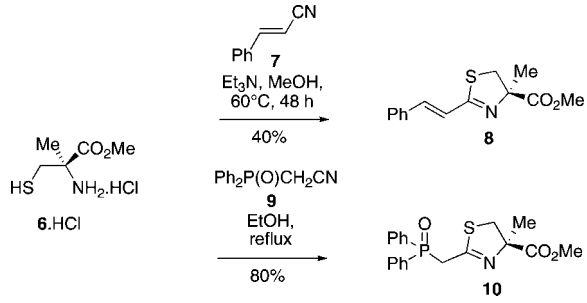
2.1.1. With Nitriles

Reaction between nitriles and amino thiols either in the presence of a base in refluxing methanol[6−8] or using zinc chloride in chlorobenzene[9] afforded the expected thiazolines. Condensation of naturally occurring (*R*)-(+)-cysteine **1a** with nitrile **2** in the presence of potassium carbonate, in methanol, at 60 °C gave chiral thiazoline **3** (Scheme 3).[6] It is worth noting that partial racemization at C-4 was observed. Ribofuranosylthiazoline **5** was obtained in good yield (90%)

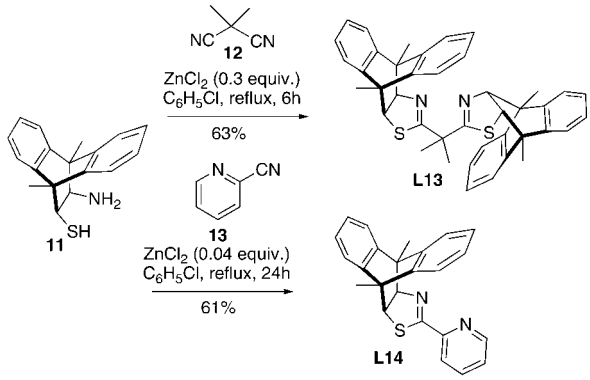
Scheme 4



Scheme 5



Scheme 6



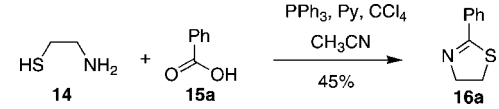
from nitrile **4** and cysteine ethyl ester hydrochloride **1b**·HCl (Scheme 4). In contrast to compound **3**, no racemization at the C-4 position was mentioned for this compound.[8] Reaction between methylcysteine ethyl ester hydrochloride **6**·HCl and cinnamonitrile **7** in the presence of triethylamine, in refluxing methanol, afforded thiazoline **8** in 40% yield (Scheme 5).[7] With phosphono acetonitrile **9** no base was required and thiazoline **10** was obtained in 80% yield (Scheme 5).[10] Both thiazolines **8** and **10** are intermediates in the total synthesis of (−)-thiangazole (see section 4). Starting from chiral amino thiol **11**, previously prepared by the authors, and dimethylmalononitrile **12** or 2-pyridylnitrile **13**, "roofed" bis(thiazoline) **L13** and pyridylthiazoline **L14** were prepared, respectively. The reaction was performed in the presence of $ZnCl_2$ in refluxing chlorobenzene (Scheme 6). Compounds **L13** and **L14** were evaluated as chiral ligands for asymmetric catalysis (see section 5).[9]

2.1.2. With Carboxylic Acids and Esters

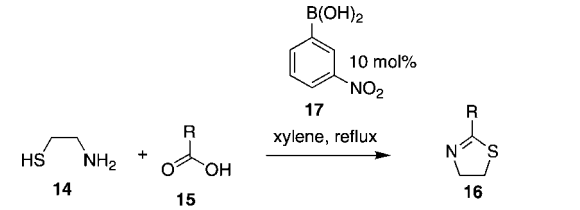
In the early 1980s the synthesis of thiazoline **16a** was reported. Benzoic acid **15a** and aminoethanethiol **14** were reacted in the presence of PPh_3, CCl_4, and pyridine, affording **16a** in 45% yield (Scheme 7).[11]

Thiazolines **16** were prepared in a parallel synthesizer by a tandem condensation−cyclodehydration of carboxylic acids

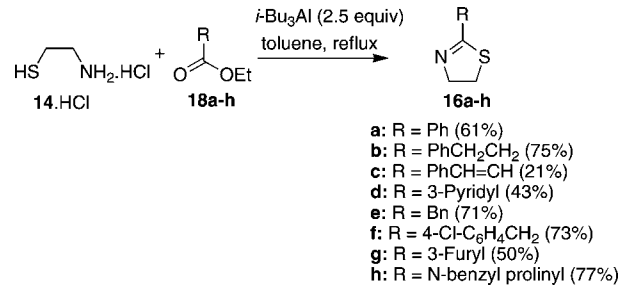
Scheme 7



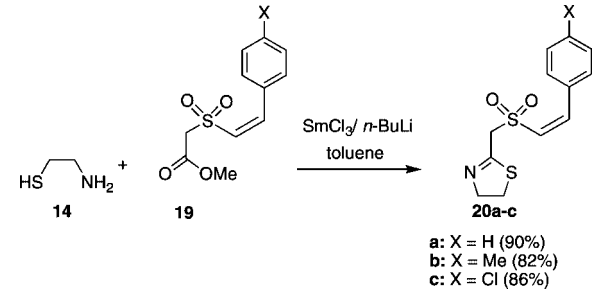
Scheme 8



Scheme 9



Scheme 10

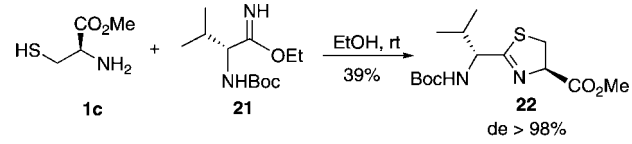


15 with aminoethanethiol **14** using 3-nitrophenylboronic acid **17** as a dehydration catalyst[12] (Scheme 8).

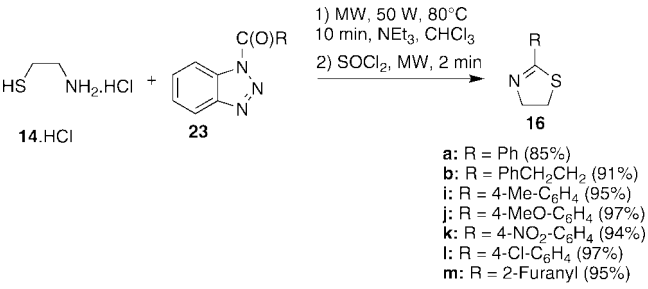
In a more general approach a large variety of 2-thiazolines **16** was prepared in moderate to good yields by condensation of aminoethanethiol hydrochloride **14**·HCl with aryl, heteroaryl, and alkyl esters **18** in the presence of triisobutylaluminium (2.5 equiv), which activates the carbonyl group (Scheme 9).[13] This one-step procedure showed a wide tolerance to functional groups. The authors explained the lowest yield (21%) obtained with ethyl cinnamate **18c** by a competing Michael addition reaction. With 3-pyridyl ester **18d** isolation of a small amount (8%) of pyridyl amide disulfide suggested initial attack of the carbonyl by the nitrogen nucleophile followed by attack of the sulfur nucleophile promoting cyclization to afford **16d**.

Z-Styryl sulfonylacetate **19** was condensed to aminoethanethiol **14** in the presence of samarium chloride and *n*-butyllithium leading to novel 2-(2-aryl-ethenesulfonylmethyl) thiazolines **20** (Scheme 10).[14] The reaction involved nucleophilic attack of the thiol on the $SmCl_3$-activated carbonyl carbon.

Scheme 11



Scheme 12



2.1.3. With Iminoethers

Pattenden and North proposed the condensation of β-amino thiols with iminoethers derived from N-protected chiral amino acids. As an example, thiazoline **22** was prepared in 39% yield by reacting N-Boc iminoether **21**, derived from L-valine, with cysteine methyl ester **1c** (Scheme 11).[15] Racemization at the thiazoline chiral center was avoided (de >98%) by working up the reaction as soon as the iminoether was consumed.

2.1.4. With N-Acylbenzotriazoles

Microwave irradiation was used by Katritzky et al. to promote condensation of aminoethanethiol hydrochloride **14**·HCl with *N*-acylbenzotriazoles **23** in the presence of thionyl chloride[16] (Scheme 12). Aryl and heteroaryl 2-thiazolines **16** were obtained by this method under mild conditions in short time and high yields (85−97%).

2.1.5. With Iminium Triflates

Charette and Chua described efficient access to various 2-alkyl- and 2-aryl-thiazolines **27** from cysteine ethyl ester **1b** and secondary or tertiary amides.[17] The reactive electrophilic species is the iminium triflate **25**, which is formed by adding triflic anhydride (Tf_2O) to amides **24** in the presence of pyridine (Scheme 13). The mild conditions used are tolerant to most of the functional groups and enable preparation of highly functionalized chiral species in good yields.

2.1.6. With α,α-Difluoroalkylamines

Recently, α,α-difluoroalkylamines were used to convert amino thiols to thiazolines in good yields under mild conditions (Scheme 14).[18] 2-Phenyl and 2-*tert*-butyl thiazolines **29a** and **29b** were synthesized by this method starting from L-cysteine ethyl ester hydrochloride and the corresponding α,α-difluoroalkylamines **28a** (DFBP) and **28b** (DFMPP), respectively. It is worth noting that addition of triethylamine after addition of the difluoroalkylamine is essential to avoid racemization of the carbon bearing the carboxylate group.

2.1.7. With Aryl Ketonitriles

An efficient method to access 2-aryl-thiazolines from aminoethanethiol and aryl ketonitriles **30** under solvent-free conditions was recently described by Kamila and Biehl[19] (Scheme 15). Condensation took place under microwave irradiation. The authors proposed a mechanism that involves nucleophilic attack by the thiol followed by elimination of water to give an acrylonitrile derivative, which is then attacked via an intramolecular conjugate addition of the amino group. The expected 2-aryl-thiazolines **16** and **31** are then obtained after elimination of acetonitrile.

2.1.8. By Ru-Catalyzed Oxidation of Thiazolidines

By condensation with aldehydes under basic conditions 2-amino thiols gave thiazolidines, which are the saturated analogues of thiazolines. Duñach et al. described the synthesis of 2-thiazolines **16** and **33** by Ru-catalyzed oxidation of the corresponding thiazolidines **32** using *tert*-butylhydroperoxide (TBHP) as an oxidant (Scheme 16).[20] The reaction was carried out under mild conditions and proved to be highly selective (80−100%) considering the reasonable formation during the oxidation step of byproduct such as 3-thiazoline, thiazole, *N*-oxide, sulfoxide, or sulfone. Isolated yields are modest due in some cases to partial conversion and others to difficulty encountered during the purification process. Selected results are given in Table 1.

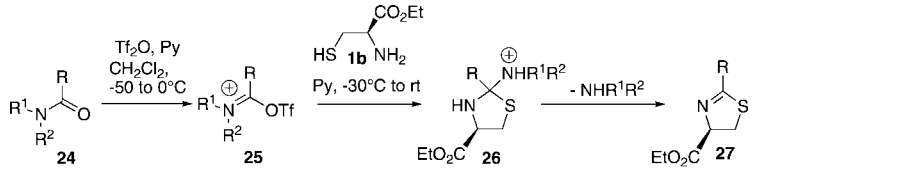
2.1.9. From S-Protected Amino Thiols

S-Benzyl-protected amino thiols were used by Heathcock for preparation of thiazolines in the total synthesis of (−)-Mirabazole C (see section 4).[21] After removal of the four benzyl protecting groups in an appropriate peptide intermediate containing three fragments coming from (*R*)-2-methylcysteine **6** and one from 2-aminoethanethiol **14**, the resulting tetrathiol **34** was treated by $TiCl_4$ to afford four thiazoline rings simultaneously (product **35**) (Scheme 17). The reaction was successfully applied to several other substrates having one, two, or three benzylsulfanyl groups. Cyclization leading to the tris-thiazoline was more sluggish than the one leading to monothiazoline or bis-thiazoline. The $TiCl_4$-mediated cyclization proved to be more difficult when the thiazoline was not substituted in the 4 position. This strategy was also used in the total syntheses of related compounds, such as (−)-thiangazole (see section 4).[10,22]

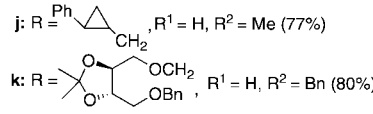
Kelly et al. used $TiCl_4$-mediated tandem deprotection−cyclodehydration of S-trityl-protected cysteine amides **36** to access thiazolines **37** in good yields (Scheme 18).[23] The main limitation of the procedure is the racemization at C(4), which depends on the aromatic ring substituent. With an electron-withdrawing group (p-NO_2) significant racemization was observed, while with an electron-donating group (p-MeO) racemization was almost suppressed. This method is useful to convert protected Cys-Cys dipeptides **38** into fused thiazole−thiazoline heterocycles such as **39**. Again racemization, which occurred at the C2-exomethine position, as observed for thiazoline **41**, is the limit of the strategy.

Recently, S-unprotected cysteine-containing dipeptides **42** were transformed into the corresponding thiazolines **43** by dehydrative cyclization using a catalytic amount of bis(2-ethyl-8-quinolinolato)dioxomolybdenum(VI). Interestingly, less than 6% of epimerization at the C2-exomethine position was observed in these conditions (Scheme 19).[24]

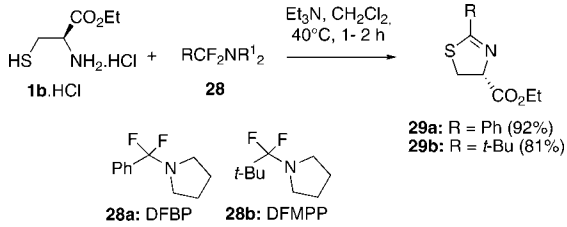
Scheme 13



a: R = $PhCH_2CH_2$, $R^1 = R^2$ = Et (90%)
b: R = $PhCH_2CH_2$, R^1 = H, R^2 = Bn (91%)
c: R = $PhCH_2CHMe$, $R^1 = R^2$ = Me (55%)
d: R = 2-Naphthyl, $R^1 = R^2$ = Et (65%)
h: R = $TBDPSO(CH_2)_3$, R^1 = H, R^2 = Me (73%)
i: R = 4-Me-$C_6H_4CO_2(CH_2)_3$, R^1 = H, R^2 = Me (76%)

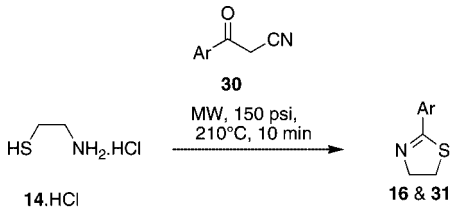


Scheme 14



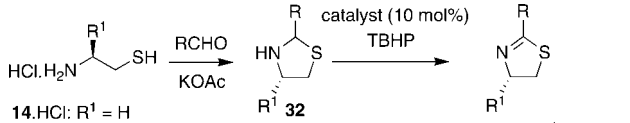
29a: R = Ph (92%)
29b: R = *t*-Bu (81%)

Scheme 15



16a: Ar = Ph (93%)
16i: Ar = 4-Me-C_6H_4 (89%)
16j: Ar = 4-MeO-C_6H_4 (98%)
16l: Ar = 4-Cl-C_6H_4 (98%)
31a: Ar = 4-F-C_6H_4 (93%)
31b: Ar = Naphth-1-yl (96%)
31c: Ar = 2,4-$(MeO)_2$-C_6H_3 (91%)
31d: Ar = 2,4-$(Cl)_2$-C_6H_3 (96%)
31e: Ar = 3,4,5-$(MeO)_3$-C_6H_2 (92%)
31f: Ar = 4-CN-C_6H_4 (85%)
31g: Ar = 4-Br-C_6H_4 (97%)

Scheme 16

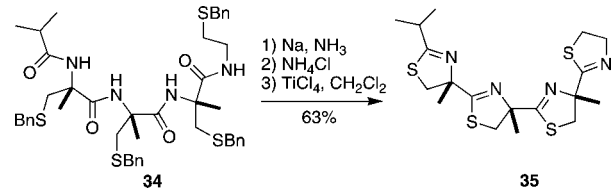


16a: R = Ph, R^1 = H
16n: R = COPh, R^1 = H
33a: R = Et, $R^1 = CO_2Et$
33b: R = Ph, $R^1 = CO_2Et$

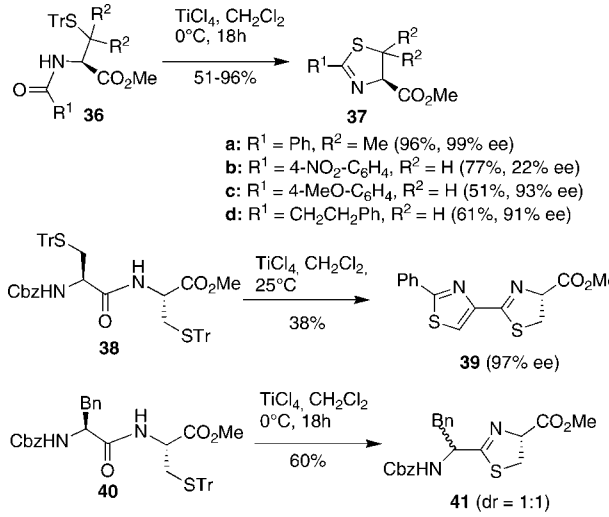
2.2. From β-Amino Alcohols

The methodologies reported in this section have the advantage of using the widely available amino alcohols as starting materials, and beyond that they offer the opportunity to prepare chiral thiazolines starting from the enantiopure amino alcohols, which are available from the chiral pool (Scheme 20). These methodologies involve (i) *N*-(β-hydroxy)thioamides[25] or (ii) oxazolines as intermediates. The *N*-(β-hydroxy)thioamides are prepared by either thionation of the corresponding *N*-(β-hydroxy)amides or direct thioacylation of β-amino alcohols. Oxazolines are prepared by a classical procedure from amino alcohols via *N*-(β-hydroxy)amides. Then, a sulfurating agent is used to convert the O atom into the S atom in either one or two steps (via an *N*-(β-hydroxy)thioamide through oxazoline ring opening), affording the expected thiazoline.

Scheme 17



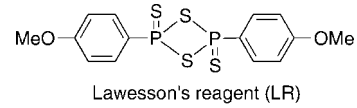
Scheme 18



a: R^1 = Ph, R^2 = Me (96%, 99% ee)
b: R^1 = 4-NO_2-C_6H_4, R^2 = H (77%, 22% ee)
c: R^1 = 4-MeO-C_6H_4, R^2 = H (51%, 93% ee)
d: $R^1 = CH_2CH_2Ph$, R^2 = H (61%, 91% ee)

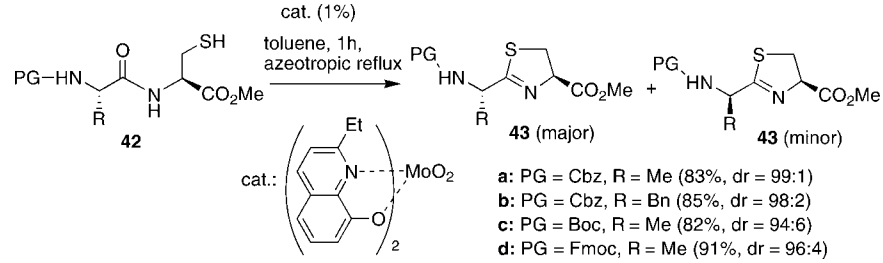
2.2.1. Using Sulfurating Agents

(a) Via Thionation of *N*-(β-Hydroxy)amides. In numerous syntheses the thiazoline heterocycle is obtained from a β-amino alcohol in three steps: acylation of the amino alcohol, thionation of the resulting *N*-(β-hydroxy)amide into *N*-(β-hydroxy)thioamide, and intramolecular cyclization (Scheme 20). The thionation is generally performed using P_2S_5[26] or Lawesson's reagent (LR).[27,28]



Lawesson's reagent (LR)

Scheme 19



Scheme 20. General Preparation of 2-Thiazolines from *β*-Amino Alcohols

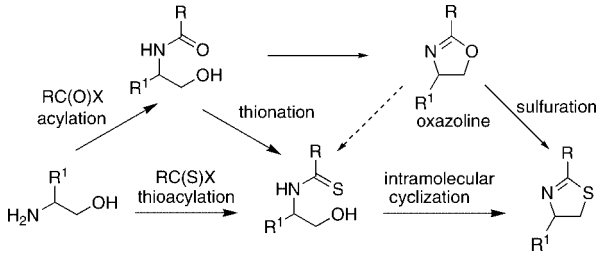


Table 1. Synthesis of Thiazolines 16 and 33 from the Corresponding Thiazolidines

product	catalyst	conditions	conv (%) of **32**	yield (%)[a]
16a	$RuCl_2(PPh_3)_2$	CH_2Cl_2, rt, 4 h	100	55
16n	$RuCl_3$/TMEDA	MeCN, rt, 4 h	100	70
33a	$RuCl_2(PPh_3)_2$	CH_2Cl_2, rt, 6 h	55	45
33a	$RuCl_3$/TMEDA	MeCN, 45 °C, 7 h	75	67
33a	$RuCl_3$/cyclam[b]	MeCN, 45 °C, 7 h	40	48
33b	$RuCl_2(PPh_3)_2$	CH_2Cl_2, rt, 4 h	94	53

[a] Yields were calculated as a function of the converted **32**. [b] Cyclam: 1,4,8,11-tetraazacyclotetradecane.

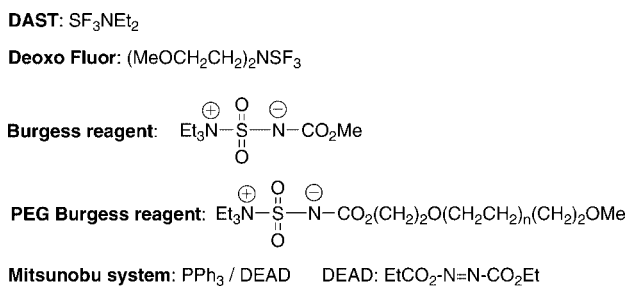


Figure 2.

After thionation, intramolecular cyclization is performed using various reagents, which have sometimes been developed for this purpose. The classical thionyl chloride ($SOCl_2$), incompatible with sensitive functionalities, can be advantageously replaced by hydroxyl activating reagents such as sulfonyl chlorides (MsCl, TsCl) or more recent reagents such as aminosulfur trifluorides (DAST,[29] Deoxo Fluor[30]), Burgess reagent,[31] and Mitsunobu system,[32] which are highly efficient under very mild conditions (Figure 2). In the selected examples reported below the ring-formation step is pointed out.

Lellouche et al.[33] described the synthesis of thiazolines **47** in three steps (acylation/thionation/cyclization) starting from amino alcohols **44** (Scheme 21). The authors showed that diethylaminosulfur trifluoride (DAST) induced fast cyclization of *N*-(*β*-hydroxy)thioamides **46** into thiazolines **47** at low temperature. The thioamide precursors **46** were previously obtained by sulfuration with LR and subsequent hydrolysis of the corresponding amido esters **45**. In the synthesis of thiazolines **50** from L-threoninate-amide **48**, which is commercially available, the silyl protection−deprotection of the hydroxyl group was required.

Mahler et al.[34] used [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor), which is thermally more stable than DAST, to promote cyclization of various *N*-(*β*-hydroxy)-thioamides **51** (previously prepared from amides using Lawesson's procedure) into thiazolines **52** (Scheme 22). In some examples (Table 2, **52d**−**f**) the authors compared the efficiency of this reagent (Method A) with the supported PEG-Burgess reagent (Method B). For **52d** and **52f** yields are higher and reaction times shorter with Deoxo-Fluor. To obtain **52e** only Deoxo-Fluor was efficient; the main product (40%) obtained with the PEG-Burgess reagent was the unsaturated compound resulting from acetic acid elimination.

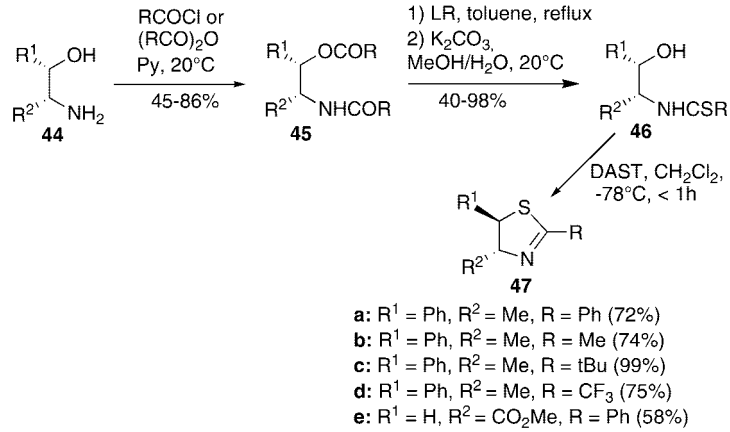
However, Burgess reagent proved to be useful for thiazolines bearing a readily racemizable stereocenter at the C(2)-exo position.[35,36] For example, in the cyclization of *N*-(*β*-hydroxy)thioamide **53** a better preservation of the stereochemical integrity at C(2) (ratio **54a/54b** > 97:3) and a higher yield were observed using Burgess reagent compared to various other cyclization agents (Scheme 23, Table 3).[35c]

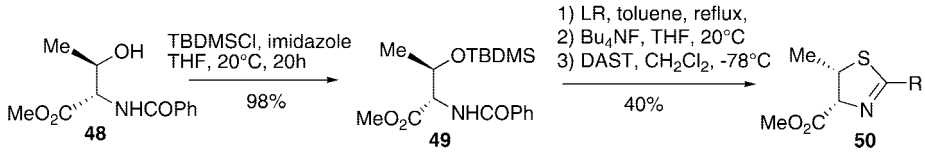
N-(*β*-hydroxy)thioamide **55**, which contains a phenol moiety, is converted into the corresponding thiazoline **56** using Burgess reagent. Due to the mild conditions used, protection of the phenol group is useless (Scheme 24).[36] Wipf and Venkatraman used a polyethylene glycol-linked Burgess reagent which induced very clean cyclodehydration with less than 2% epimerization.[37] Purification is easily performed by removal of the polymer through filtration on silica gel.

The Mitsunobu reaction[38] is also efficiently used to build various thiazolines.[39] As an example, thiazoline-containing peptides **58** are synthesized by intramolecular cyclization of the corresponding thioamides **57** (Scheme 25), which were previously obtained from silylated hydroxy-protected peptides using LR.[39a]

Although cyclizations under Mitsunobu conditions performed generally well with quantitative conversion, yields after purification sometimes decreased due to the difficulty of separation of the thiazoline products from triphenylphosphine oxide (Ph_3PO) and hydrazine derivative ($EtO_2C-NH-NH-CO_2Et$), which arise from the Mitsunobu reagents. In the synthesis of 1-methyl-NAG-thiazoline a biologically relevant compound (see section 4), *N*-(*β*-hydroxy)thioamide **59** is obtained by thionation with Lawesson's reagent of the corresponding amide. Cyclization, which involved a tertiary anomeric hydroxy group, is performed using the protic acid PPTS or the mild Lewis acid $Eu(OTf)_3$ in *N*-methylpyrrolidone (Scheme 26).[40] The authors explain the low yields (20% and 33%) in **60** by an axial position of the anomeric leaving group, which disfavors intramolecular nucleophilic substitution.

Scheme 21





Scheme 22

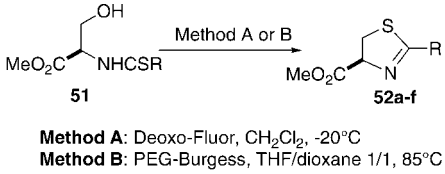


Table 2. Synthesis of Thiazolines 52 (comparison of methods A and B)

product	R	method	time	yield (%)
52a	CH(NHCO$_2$Et)Allyl	A	0.5 h	85
52b	3,4,5-(MeO)$_3$C$_6$H$_2$	A	1 h	93
52c	(3-indolyl)CH$_2$−	A	1 h	70
52d	CMe$_2$C(O)Me	A (B)	1 h (3 h)	80 (64)
52e	CHBnCHMe(OMe)	A (B)	0.5 h (8 h)	90 (0)
52f	CH$_2$CMe$_3$	A (B)	2 h (2 h)	85 (71)

Scheme 23

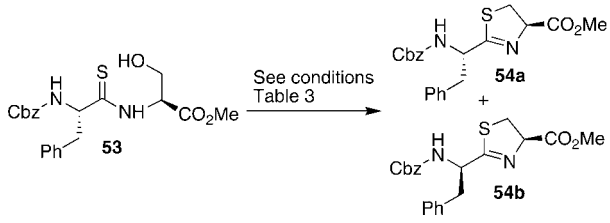
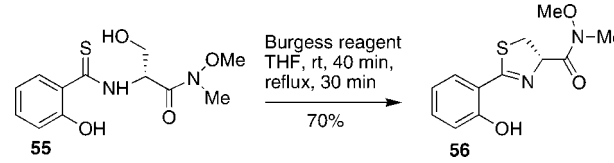


Table 3. Comparative Cyclization Conditions of Thioamides 53 into Thiazolines 54

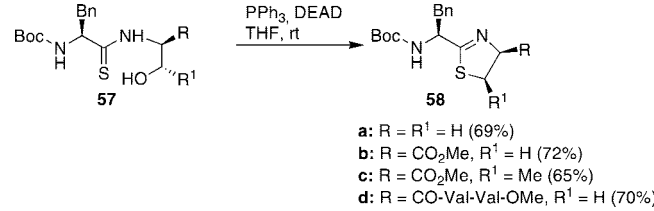
conditions	yield (%)	ratio **54a**:**54b**
TsCl, Et$_3$N, CH$_2$Cl$_2$, 42 °C, 1 h	40	1:1
(i) SOCl$_2$, 0 °C, 2 h; (ii) Py, THF, 0 °C, 15 min	49	1:1
PPh$_3$, DIAD, CH$_2$Cl$_2$, −78° to −22 °C, 30 min	80	78:22
Burgess reagent, THF, 65 °C, 10 min	96	>97:3

In some cases, the sulfurating agent is able to promote a one-pot thionation/cyclization of *N*-(*β*-hydroxy)amides or *N*-(*β*-halo)amides, leading directly to thiazolines.[41−44] For example, chiral thiazoline ligands **L4** and **L6** (see section 5) were obtained by this method from bis[*N*-(*β*-hydroxy)amide] **61** (Scheme 27). In a preliminary study, the reaction

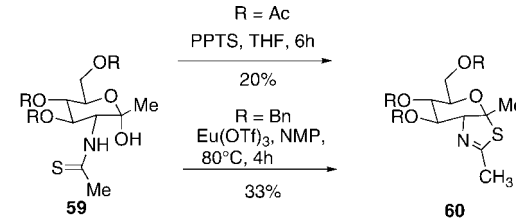
Scheme 24



Scheme 25



Scheme 26



conditions were optimized for ligand **L4e** (Table 4, entries 1−3). The best yield was obtained using P_2S_5 in the presence of triethylamine in refluxing toluene for 4 h (entry 3). These conditions were then applied to the synthesis of other derivatives **L4**.[42] Ligands **L6** were obtained under similar conditions using P_2S_5 in refluxing pyridine for 22 h (Table 4, entries 7−11).[43]

(b) Via Sulfuration of Oxazolines. Another approach to thiazolines from amino alcohols involves conversion of oxazolines into thiazolines. The reaction can be performed in one step using the sulfuration of oxazolines with P_2S_5[41] or two steps through oxazoline ring opening by sulfhydrolysis with H_2S and subsequent intramolecular cyclization of the thioamide.[45,35a] 2-Methyl thiazolines **63** were obtained in modest yields (32−49%) by direct sulfuration of 2-methyl

Scheme 27

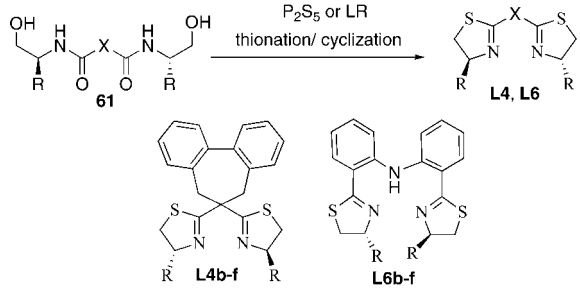
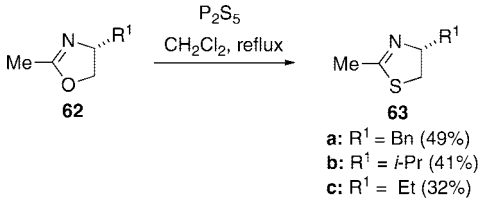


Table 4. Thionation/Cyclization Conditions of Amides 61 into Thiazolines L4[42] and L6[43]

entry	conditions	R	product	yield (%)
1	LR, THF, NEt_3, reflux, 4 h	Bn	**L4e**	20
2	P_2S_5, Py, reflux, 6 h	Bn	**L4e**	40
3	P_2S_5, toluene, NEt_3, reflux, 4 h	Bn	**L4e**	60
4		*i*-Bu	**L4f**	51
5		*i*-Pr	**L4b**	50
6		Ph	**L4d**	81
7	P_2S_5, Py, reflux, 22 h	*i*-Pr	**L6b**	54
8		*i*-Bu	**L6f**	47
9		Ph	**L6d**	47
10		Bn	**L6e**	82
11		*t*-Bu	**L6c**	57

Scheme 28



oxazolines **62** with P_2S_5 in boiling dichloromethane (Scheme 28).[41] To prepare the corresponding 2-phenyl and 2-*tert*-butyl thiazolines derivatives, the authors preferred converting the *N*-(β-hydroxy)amides into thioamides. Good yields were obtained (59−96%) in this step.

The ring opening of amide oxazoline **64** with H_2S followed by cyclization of the *N*-(β-hydroxy)thioamide intermediate **66** using the Burgess reagent led to thiazoline **67** in 85% overall yield (Scheme 29).[35b]

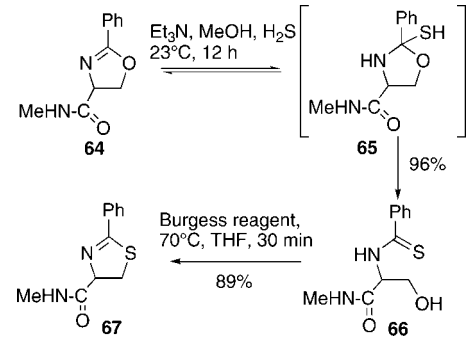
These methodolgies (section 2.2.1), although quite general, have a major drawback: use of a sulfurating agent (P_4S_{10}, LR, H_2S), which is difficult to handle, does not tolerate numerous functional groups, requires drastic conditions, and is difficult to workup. Therefore, more convenient approaches using thioacylating agents have been developed.

2.2.2. Using Thioacylating Agents

The key precursors to thiazolines, i.e., the *N*-(β-hydroxy)-thioamides, can be obtained more conveniently and directly from amino alcohols and thioacylating compounds, thus avoiding the use of nasty sulfurating reagents.

In the first example reported the authors described the use of commercially available dithiooxamide **69** as thioacylating agent to synthesize 2,2′-bis(thiazoline) **71** from β-amino alcohols **68** (Scheme 30).[46] Helmchen et al. also used this method to synthesize the chiral bis(thiazoline) ligands **L1**, which were tested as ligands for asymmetric catalysis (see section 5). For example, dithiooxamide **69** reacts with various chiral amino alcohols **72** to give bis(thioamides) **73**, which

Scheme 29



after intramolecular cyclization using thionyl chloride yields bis(thiazolines) **L1** in modest yields (Scheme 30).[47]

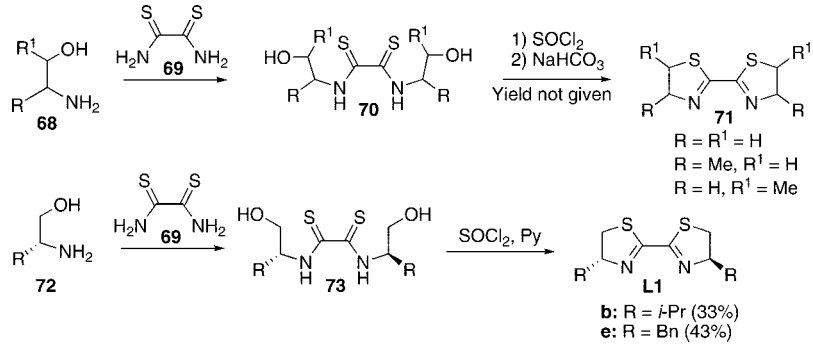
In 2000 Masson et al. developed a general and efficient method to prepare thiazolines using dithioesters as *N*-thioacylating agents. Thus, thiazolines can be easily obtained from amino alcohols using dithioester as the sulfur source.[48] The reaction proceeds in two steps: thioacylation followed by intramolecular cyclization. Thioacylation of amino alcohols with dithioesters can be performed in most cases under mild conditions by simply mixing the reagents at room temperature. For the second step, intramolecular cyclization, reagents and reaction conditions are similar to those already described in the previous section. This methodology was first applied to the synthesis of chiral thiazoline-phosphonates **78** from phosphonodithioacetate **74** and commercially available enantiopures β-amino alcohols.[48a] The reaction was then applied to difluorinated[48b] phosphonate derivative **75**, which led to thiazolines **79** (Scheme 31). Reaction conditions and yields are given in Table 5.

When difluorinated phosphonate **75** is reacted with 2-amino-1,3-ethanediol intramolecular cyclization of the resulting thioamide **80** using 2 equiv of MsCl leads to mesylate-functionalized thiazoline **81a**. Starting from thioamide **80** and using Mitsunobu conditions, one-pot cyclization, and subsequent introduction of a nucleic base afford new nucleotide analogues **81b,c** (Scheme 32).[48b]

This method is also applicable to sugar-dithioester substrate **82** leading to thiazoline-containing mannofuranose derivative **83** (Scheme 33).[48d] Although the thioacylation performed well (84% yield) and cyclization was quantitative, the overall yield was rather low (30%), mainly because of the difficult separation of the thiazoline from triphenylphosphine oxide and the hydrazine derivative arising from the Mitsunobu reagents.

Nevertheless, the versatility of the method was clearly demonstrated by preparation of a large variety of thiazoline ligands, analogous of the well-known oxazolines.[48c,e] The structural family of the prepared thiazolines includes bis(thiazolines), pyridyl- and quinolyl-thiazolines, and phosphine-thiazolines (see section 5, Figure 19: **L2**, **L3**, **L7**−**L10**, and **L12**). As an example, synthesis of C_2-symmetric bis(thiazolines) **L2** ($R^1 = R^2$) is reported below (Scheme 34). Quantitative thioacylation was performed without solvent at room temperature. Intramolecular cyclization occurred after mesylation under classical conditions. This procedure, starting from isopropyl dithioester **84** and leading to bis(thiazolines) in five steps, has the advantage of enabling the independant and consecutive synthesis of the two thiazoline rings, offering the opportunity to access nonsymmetric bis(thiazolines) **L2′** using two different amino alcohols (R^1, R^2).[49]

Scheme 30



Scheme 31

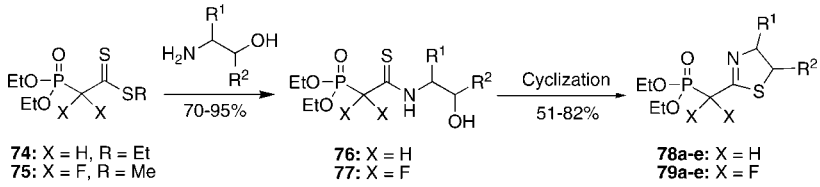
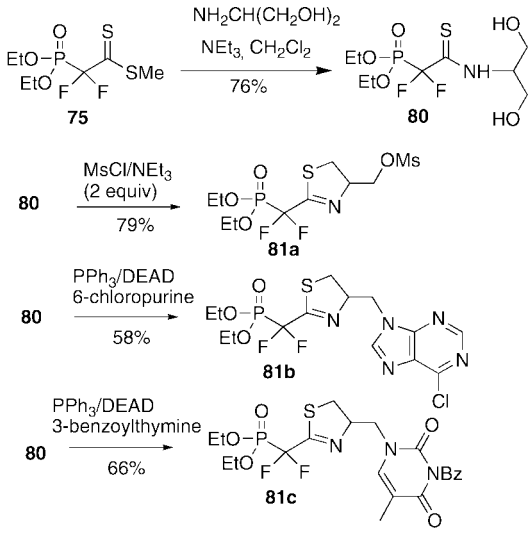


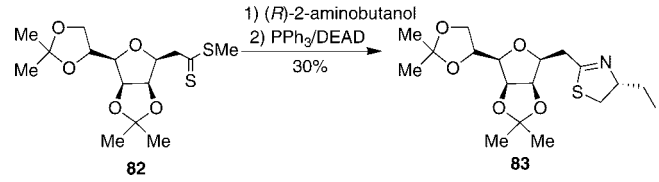
Table 5. Cyclization Conditions for the Synthesis of Thiazolines 78 and 79

dithioester	amino alcohol	R^1, R^2	cyclization conditions	product	yield (%)
74	1-ethanolamine	H, H	PPh_3/ DEAD	**78a**	51
74	*R*-(−)-2-aminobutanol	Et, H	PPh_3/ DEAD	**78b**	78
74	*S*-(+)-valinol	*i*-Pr, H	PPh_3/ DEAD	**78c**	76
74	*R*-(+)-phenylglycinol	Ph, H	PPh_3/ DEAD	**78d**	55
74	*S*-(−)-phenylalaninol	Bn, H	PPh_3/ DEAD	**78e**	61
75	1-ethanolamine	H, H	$SOCl_2$/Py	**79a**	82
75	*R*-(−)-2-aminobutanol	Et, H	$SOCl_2$/Py	**79b**	85
75	*R*-(+)-phenylglycinol	Ph, H	$SOCl_2$/Py	**79c**	80
75	*rac*-serine methyl ester	CO_2Me, H	$SOCl_2$/Py	**79d**	77
75	(1*S*,2*R*)-(+)-norephedrine	Me, Ph	$SOCl_2$/Py	**79e**	82

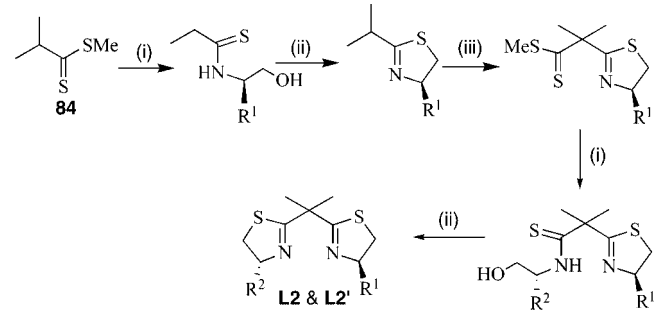
Scheme 32



Scheme 33



Scheme 34

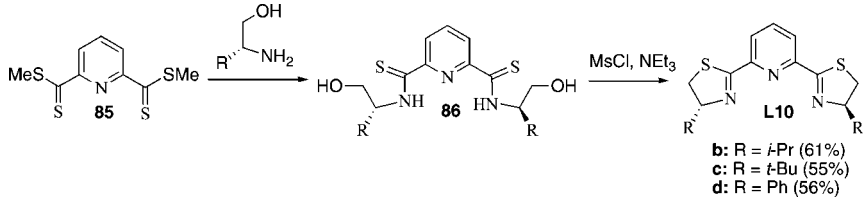


In the synthesis of chiral pyridine bis(thiazoline) ligands **L10**[48c,e] the two thiazoline cycles are formed simultaneously using 2,6-pyridine bis(dithioester) **85** as a bis(thiocarbonyl) reagent for the amino alcohol thioacylation. The obtained bis(thioamides) **86** led to pyridine bis(thiazolines) **L10** via the classical mesylate cyclization (Scheme 35).

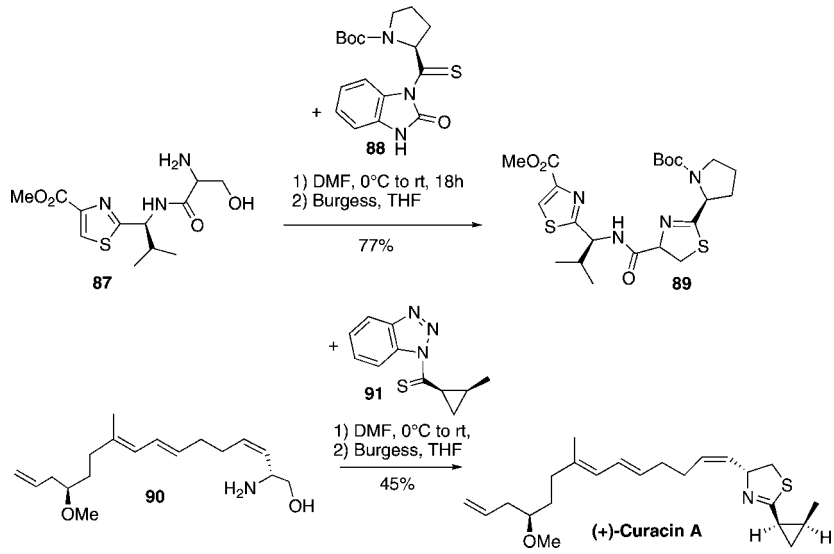
The only limitation of this method involving dithioester thioacylating reagents is the accessibility of the dithioester precursor. Nevertheless, the various existing procedures to synthesize such compounds offer access to a reasonable number of thiazoline structures.[50]

More sophisticated thioacylating agents, such as proline thiocarbonyl derivative **88** and benzotriazole cyclopropyl thioamide **91**, were used by Pattenden et al. to form the thiazoline ring in the total syntheses of trunkamide A[51] and curacin A,[52] respectively (see section 4). These thioamides were previously obtained by reaction of the corresponding

Scheme 35



Scheme 36



amides with P_4S_{10}. After thioacylation of amino alcohol **87** with reagent **88** and amino alcohol **90** with reagent **91**, subsequent intramolecular cyclizations were performed in both cases using the Burgess reagent, leading to thiazoline **89** and curacin A, respectively (Scheme 36).

2.3. Miscellaneous

Less general approaches have also been reported for the synthesis of functionalized derivatives. Some methods involve primary thioamides, which mainly react by nucleophilic attack through the sulfur atom. For example, phosphine-catalyzed annulation of aryl-thioamides **93** with 2-alkynoates **92** provided 2-aryl-thiazolines **94** in moderate to good yields (Scheme 37).[53] The reaction is especially of interest with aryl and heteroaryl thioamides.

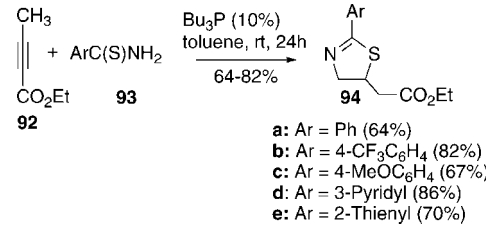
5-Spirocyclopropyl thiazolines **98** were prepared in two steps under basic conditions starting from thioamides **96** and 2-chloro-2-cyclopropylideneacetates **95** via nucleophilic attack of the sulfur atom to the Michael acceptor **95** followed by intramolecular substitution (Scheme 38).[54] With $R^1 \neq H$, mixtures of two or three diastereomers were obtained.

2-Thiazolin-4-ones **102** (in equilibrium with their isomers **103**) were obtained by spontaneous cyclization of hydrazones **101**, which resulted from reaction between 1,2-diaza-1,3-butadienes **99** and thioamides **100** (Scheme 39).[55]

Various cycloalkyl-thiazolines **106** have been obtained by reaction between cycloalkenyl-1-diazenes **104** and thioamides **105** and then converted into fused cycloalkyl-thiazoline-pyrazole systems **107** (Scheme 40).[56]

2-(β-Oxo)-2-thiazolines **111**, in particular cyclic derivatives, were prepared under mild conditions with moderate yields by reaction between enamines **109** and 2-chloroethyl isothiocyanate **108** followed by subsequent one-pot hydrolysis (Scheme 41).[57]

Scheme 37

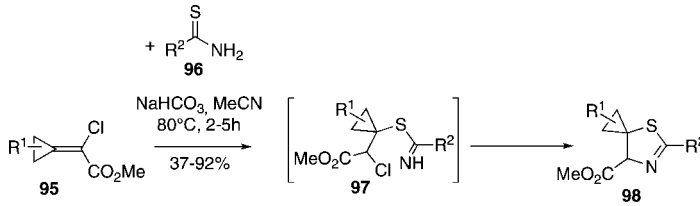


An original approach was used by Fukuyama and Xu for synthesis of the thiazoline ring in the total synthesis of (−)-tantazole B.[58] Appropriate lactone **112** was opened with thioisobutyric acid to give thioisobutyric ester **113**. Upon heating in refluxing benzene this compound afforded the desired thiazoline bearing a carboxylic acid group, which was somewhat unstable and immediately converted into carboxylic thioester **114** (Scheme 42).

Vicinal azido-thioethers can be converted into thiazolines using PPh_3 via a sequential one-pot Staudinger reduction/aza-Wittig reaction.[59,60] This method, which takes place under mild conditions, is particularly useful for acid-sensitive substrates such as thiazoline-containing peptides. For example, starting from azido-thioester **115**, the method was used in the synthesis of thiazoline **116** (Scheme 43), which is part of various modified structures of apratoxin, a natural cyclopeptide (see section 4, Figure 7).[60]

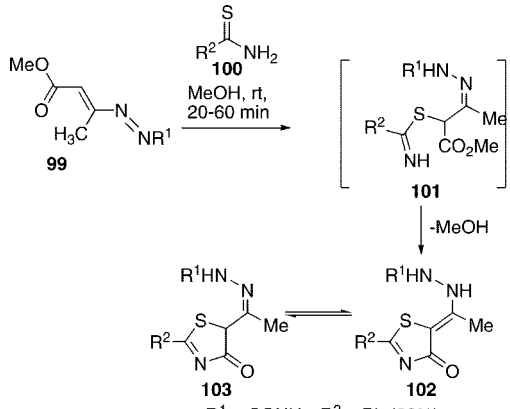
Bridgehead-fused norbornanethiazolines **118** were synthesized in two steps from thiocamphor **117a** and thiofenchone **117b**, which were previously obtained from the corresponding commercially available (1*R*)-(+)-camphor and (1*R*)-(−)-fenchone.[61] The key step of the sequence is stereoselective trapping of the 1-(trifluoromethylsulfonylthio)-2-norbornyl cation by nitriles followed by intramolecular cyclization (Scheme 44).

Scheme 38



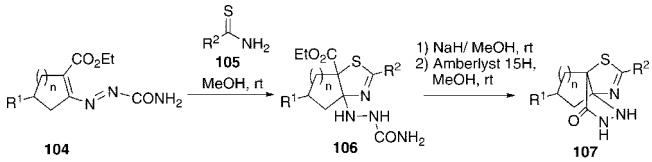
a: R^1 = H, R^2 = Ph (86%)
b: R^1 = H, R^2 = 4-MeO-C_6H_4 (92%)
c: R^1 = H, R^2 = 4-F-C_6H_4 (67%)
d: R^1 = H, R^2 = NMePh (39%)
e: R^1 = Me, R^2 = Ph (51%, dr = 1.2/1)
f: R^1 = Me, R^2 = 4-Br-C_6H_4 (52%, dr = 9.3/1.5/1)
g: R^1 = Et, R^2 = Me (78%, dr = 1.7/1/1)

Scheme 39



a: R^1 = $CONH_2$, R^2 = Ph (88%)
b: R^1 = $CONH_2$, R^2 = 3-Py (68%)
c: R^1 = CONHPh, R^2 = Ph (73%)
d: R^1 = CO_2Me, R^2 = Ph (70%)
e: R^1 = CO_2t-Bu, R^2 = Ph (73%)

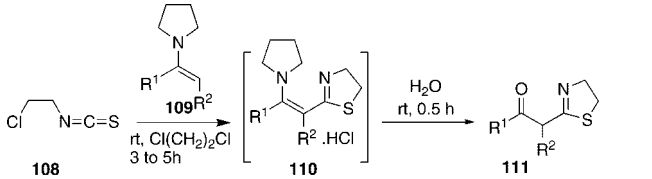
Scheme 40



a: n = 1, R^1 = H, R^2 = 2-MeO-C_6H_4 (91%)
b: n = 2, R^1 = H, R^2 = C_6H_5 (93%)
c: n = 2, R^1 = Me, R^2 = C_6H_5 (92%)

a: 54%
b: 63%
c: 62%

Scheme 41



a: R^1,R^2 = $(CH_2)_3$ (38%)
b: R^1,R^2 = $(CH_2)_4$ (61%)
c: R^1,R^2 = $(CH_2)_5$ (30%)
d: R^1,R^2 = $(CH_2)_2NMeCH_2$ (40%)
e: R^1 = Et, R^2 = Me (32%)

The enantiomers of thiazoline **122** have been synthesized by intramolecular deselenylation−cyclization of the two corresponding β-seleniated thioamide diastereomers **121**, which were previously obtained by treatment of the corresponding amides with LR (Scheme 45).[62] The chiral β-seleniated amides precursors **120** were prepared in two steps starting from camphor diselenide **119** (as chiral auxiliary), nitriles, and alkenes.

Selenium-mediated 5-exotrig cyclizations of allylic thioamides **124** (obtained from the corresponding amides **123** with LR) led to 2-thiazolines **125**, which carry a phenylselenylmethyl substituent in the 5 position (Scheme 46).[63] When cyclizations of **124** were performed in the presence of a catalytic amount of *p*-toluensulfonic acid instead of phenylselenyl bromide thiazolines **126** were obtained.

Flash vacuum pyrolysis (FVP) of 3-thioacyloxazolidin-5-ones at 550 °C led cleanly, by loss of CO_2, to 2-thiazolines.[64] An example involving the oxazolidinone **127** derived from *S*-valine is shown in Scheme 47. The thiazoline was obtained as a mixture of two diastereomers **128a** and **128b** in 28% and 17% isolated yield, respectively.

3. Reactivity and Synthetic Applications of 2-Thiazolines

The reactivity of thiazolines arises from the two nucleophilic centers localized on the nitrogen atom and the sulfur atom and from the electrophilic center on the carbon of the C═N bond. A supplementary nucleophilic center can arise after deprotonation if the thiazoline has a hydrogen atom on the carbon in the α position. Therefore, thiazolines are versatile reagents for the synthesis of various compounds such as carbonyl, thiazoles, β-amino thiols, or thiazolinium salts (Figure 3).

The thiazoline heterocycle can be preserved or altered depending on the target to be reached. Reactions in which the thiazoline heterocycle is preserved are mainly related to the acidity of the proton in the α position to 2-alkyl-2-thiazolines. Upon treatment with a base the resulting carbanion can react with different electrophiles, leading to various functionalized thiazolines such as thiazoline phos-

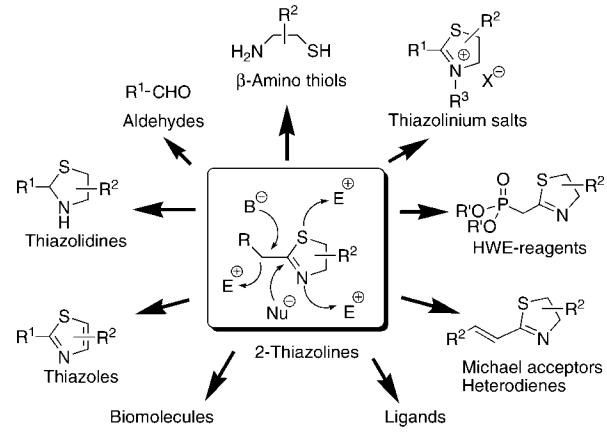
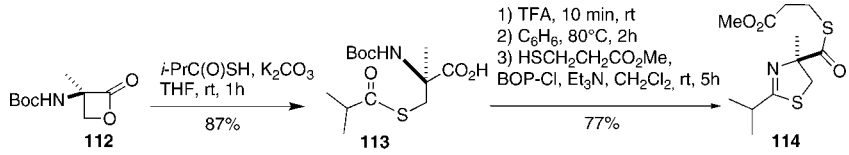
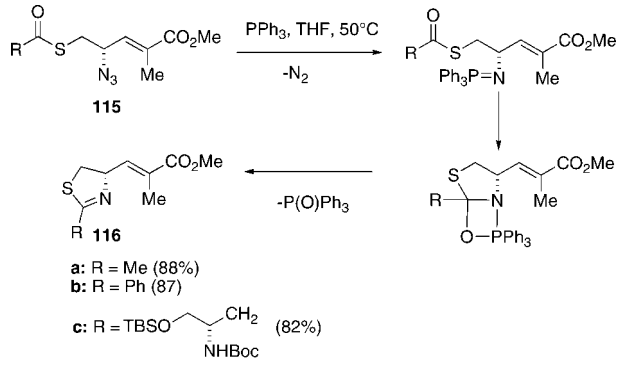


Figure 3. Reactivity and synthetic applications of 2-thiazolines.

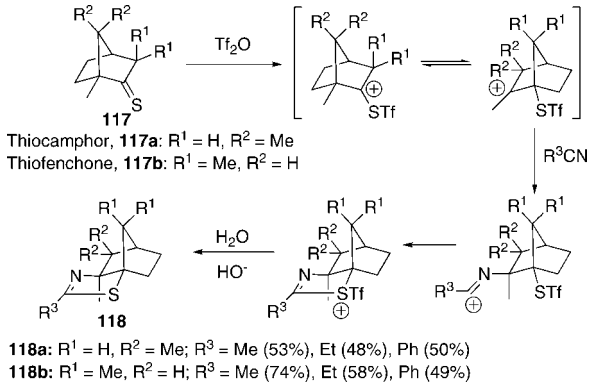
Scheme 42



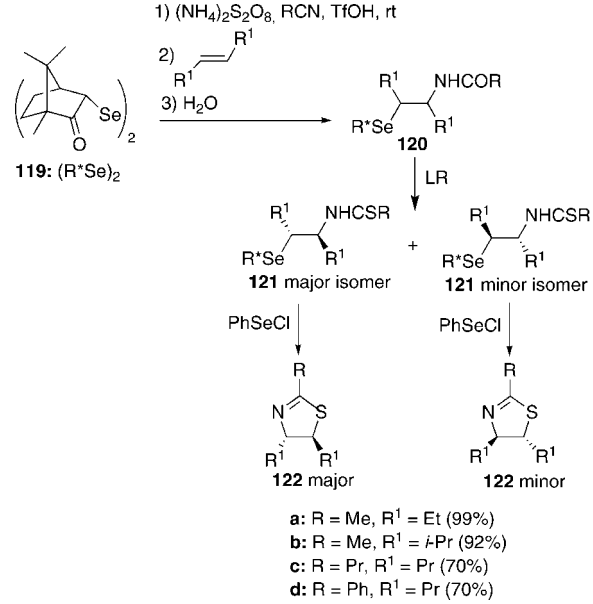
Scheme 43



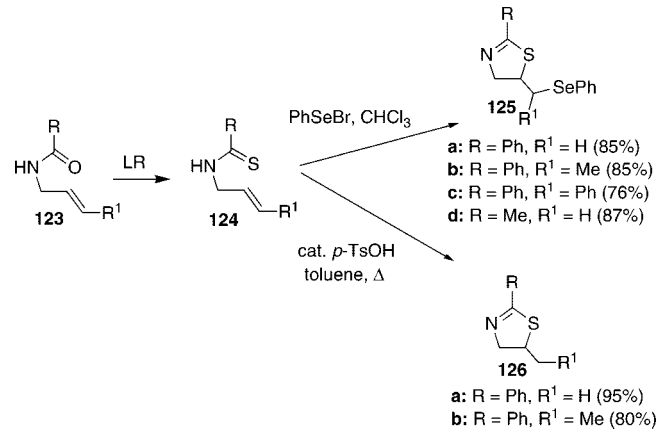
Scheme 44



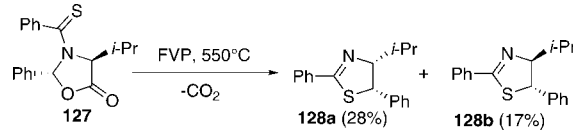
Scheme 45



Scheme 46



Scheme 47

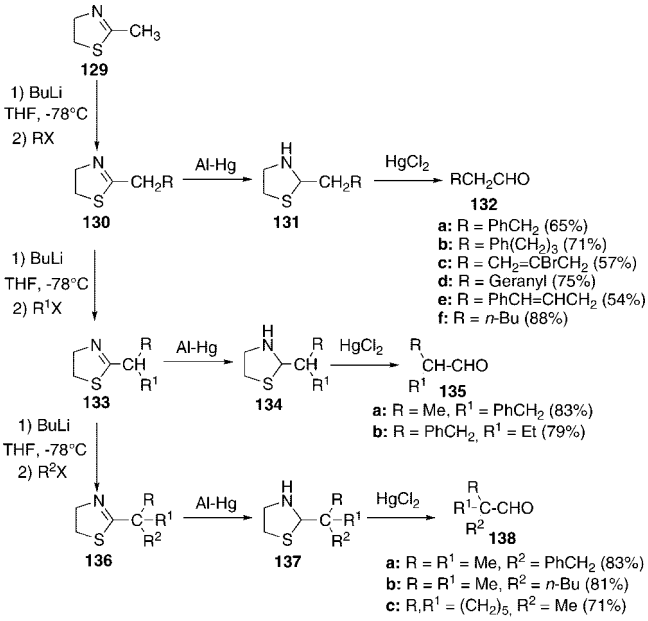


phonates, which are useful synthetic intermediates as Horner−Wadsworth−Emmons (HWE) reagents or vinyl thiazolines, which are Michael acceptors or heterodienes. Depending on the structure of the thiazolines, the modifications can also affect the substituents or functions on the thiazoline ring with preservation of the heterocyclic structure (Michael additions to vinyl thiazolines, ortho-metalation of 2-aryl-thiazolines, and other reactions involving functionalities present on the thiazoline heterocycle). Protonation and alkylation on the thiazoline nitrogen atom giving thiazolinium salts can also be classified in this last category. Moreover, thiazolines possessing a chiral center in the 4 or/and 5 position can be used as chiral auxiliaries or building blocks for preparation of more complexes chiral structures, such as thiazoline-containing biomolecules (see section 4) or chiral ligands for asymmetric catalysis (see section 5). In various other reactions the thiazoline ring is altered: oxidation, reduction, ring-opening reaction, and cycloadditions involving the C═N bond. They allow the preparation of various useful compounds such as carbonyl derivatives, β-amino thiols, thiazoles, or thiazolidines. Since synthetic applications of 2-thiazolines often involve more than one of the different reactive sites, we classified them by type of compounds obtained more than by type of reactions involved.

3.1. Synthesis of Aldehydes and Ketones

One of the main applications of thiazolines is their use as masked aldehydes. Thiazoline-masked form is complementary to the oxazoline-masked form since release of the aldehyde function proceeds under different conditions for the two species. Typically, with oxazoline the nitrogen atom is first quaternized and then borohydride reduction and subsequent hydrolysis of the resulting oxazolidine under mild acidic conditions lead to the free aldehyde.[2a] Starting from thiazolines the synthesis of aldehydes involves two main steps: reduction of thiazoline ring into thiazolidine and

Scheme 48



cleavage to aldehyde. This methodology was developed by Meyers, who synthesized a series of aldehydes starting from 2-methyl-thiazoline **129**.[65] Deprotonation of **129** in the α position followed by quenching with various alkyl halides and reduction using aluminum amalgam led to thiazolidines **131**, which were finally cleaved with mercuric chloride to give alkyl-substituted aldehydes **132**. Moreover, the possibility to deprotonate the 2-alkyl-2-thiazolines in the α position and subsequent reaction with an electrophile allows access to various functionalized aldehydes. The sequence can be repeated once or twice to obtain di- or trialkyl-substituted aldehydes **135** and **138**, respectively (Scheme 48). Good yields for the alkylation step (80−95%) are obtained if alkyl iodides and benzyl or allyl chlorides or bromides served as alkylating agents. Reduction is then performed using freshly prepared aluminum amalgam in wet ether at reflux for 1−2 h, affording in quasi-quantitative yields thiazolidines **131**, **134**, and **137**. The crude derivatives were then directly cleaved with mercuric chloride in acetonitrile/water (4/1), affording the expected aldehydes **132**, **135**, and **138** in reasonable to good yields (54−88%).

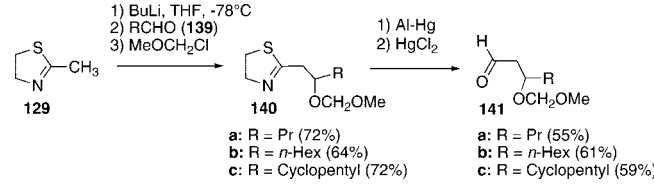
This method was extended to the preparation of β-hydroxy-protected aldehydes by reacting α-deprotonated 2-methyl-2-thiazoline **129** with an aldehyde **139** (Scheme 49). The methoxymethyl protecting group was found to be the more convenient for both trapping the lithium alcoholate and the cleavage step, leading to β-(methoxymethyloxy)aldehydes **141** in good yields.[66]

Thiazoline−thiazolidine transformation and subsequent cleavage with $HgCl_2$ were extended to the preparation of α,α-disubstituted β-ethylenic ketones.[67] The β-ethylenic thiazolidine precursors **144** were obtained by addition of allylic Grignard reagent **143** to 2-alkyl-2-thiazolines **142**. Conventional mercuric chloride cleavage afforded the expected ketones **145** (Scheme 50).

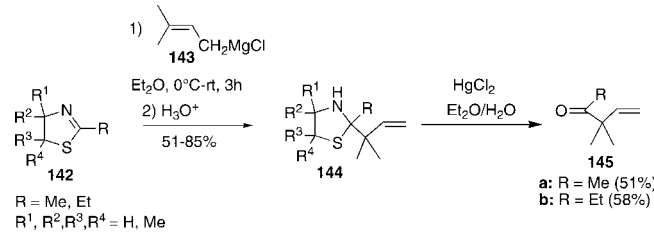
3.2. Synthesis of Thiazoles

The importance of thiazoles as useful synthetic tools in organic chemistry and as a structural part of biologically active compounds is well established.[68] Thiazolines can be

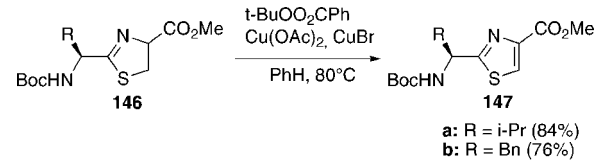
Scheme 49



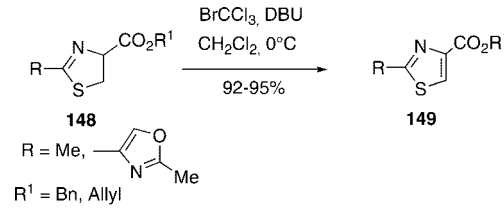
Scheme 50



Scheme 51



Scheme 52



easily converted into thiazoles using different oxidizing systems. 2-Thiazolines **146** containing various substituents in the α position were oxidized with *tert*-butylperoxybenzoate in the presence of a mixture of Cu(I) and Cu(II) salts into the corresponding thiazoles **147** (Scheme 51).[69] Under these conditions the sensitive amino functions as well as the stereochemical information were preserved.

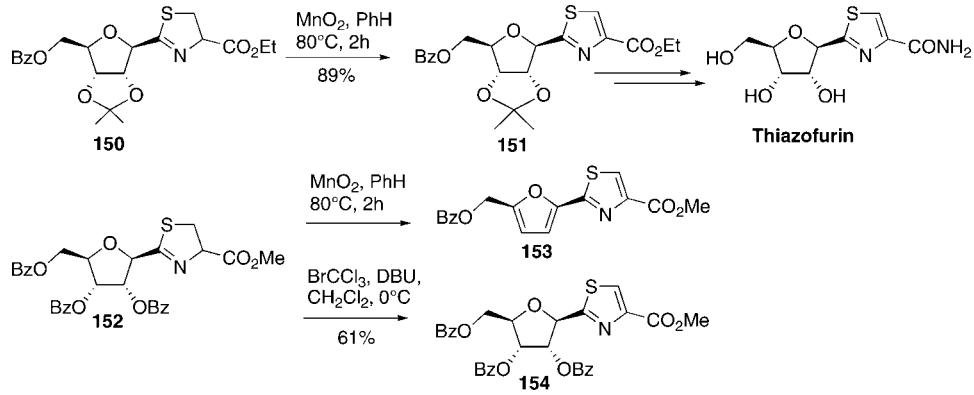
Use of the $BrCCl_3$/DBU system as oxidant to convert thiazolines **148** into thiazoles **149** also gave high yields, leaving unchanged the benzyl or the allyl ester group present in the substrate (Scheme 52).[70]

In the synthesis of thiazofurin,[71] a well-known antitumoral agent, the intermediate (β-ribofuranosyl)thiazoline **150** was oxidized into the corresponding thiazole **151** using activated MnO_2 in benzene (Scheme 53).[8] The acetonide protection was necessary since using the 2′,3′-benzoate derivative **152** as substrate afforded the thiazole-furan **153**.

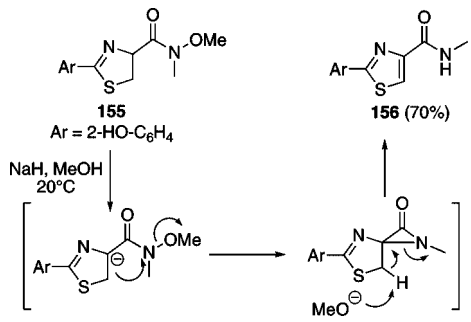
On the other hand, **152** could be successfully transformed into thiazole **154** using bromotrichloromethane and DBU.[72]

A new base-induced high-yielding reaction for the thiazoline−thiazole conversion was applied in the synthesis of a pyochelin siderophore analogue (see section 4, Figure 10).[73] In the presence of an excess of sodium hydride in methanol, 2′-(2-hydroxyphenyl)-thiazoline-4′-(*N*-methoxy-*N*-methyl) carboxamide **155** was transformed in a good yield (70%) into the 2′-(2-hydroxyphenyl)-thiazole-4′-*N*-methyl carboxamide **156**. The mechanism proposed by the authors is depicted in Scheme 54.

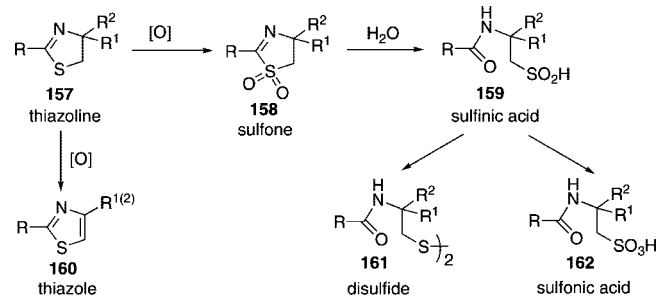
Scheme 53



Scheme 54



Scheme 55



Aitken studied the behavior of thiazolines **157** toward various oxidation systems. Mixtures containing cyclic products (thiazole **160**, sulfone-thiazoline **158**) or opened-ring products (sulfinic and sulfonic acids **159** and **162**, disulfide **161**) were obtained depending on both the oxidant (Oxone, mCPBA, $KMnO_4$, H_2O_2, peracides, oxaziridines) and the reaction conditions used (Scheme 55).[41] Selected examples are shown in Table 6. In most cases, low yields in a single product, or mixtures of products were obtained. However, by using 1 equiv of benzoic acid and 1.5 equiv of $KMnO_4$ under phase-transfer conditions (PTC: CH_2Cl_2/H_2O and catalytic $BnEt_3N^+Cl^-$), the conversion of thiazolines **157** into the corresponding sulfones **158** was performed with excellent yields (90%). Thiazoles **160** were never obtained cleanly whatever the conditions and oxidant used.

Table 6. Oxidation of Thiazolines 157

R	R^1	R^2	oxidant	products (%)
Me	Bn	H	oxone	**161** (24%)
Ph	Bn	H	mCPBA	**162** (53%)
Ph	H	Et	H_2O_2	**160** (19%), **161** (5%), **162** (19%)
Ph	*i*-Pr	H	oxaziridine: PhCH-(O-NSO_2Ph)	**158** (23%), **162** (23%)
Ph	H	Et	$KMnO_4$	**158** (90%)
Ph	H	Et	AcOOH	**162** (15%)

3.3. Synthesis of β-Amino Thiols

Although useful as synthetic intermediates, only two 2-amino thiols, that is, the achiral cysteamine and the cysteine (in both racemic and enantiopure forms) are widely commercialized. Therefore, developing efficient and general methods allowing for the preparation of various amino thiols is of interest. Thiazoline ring opening by acidic hydrolysis represents an elegant method to prepare 2-amino thiols.

Opening of the thiazolines ring by acidic hydrolysis was studied as early as 1959,[74,75] mainly because of the presence of the thiazoline heterocycle in many biologically active natural compounds. The proposed mechanism for ring opening involves attack of water on the thiazolinium salt **164**, leading to a 2-hydroxythiazolidine intermediate **165**, which then gives *N*-acyl or *S*-acyl 2-amino sulfanyl derivatives **166** or **167** depending on the conditions used (Scheme 56).

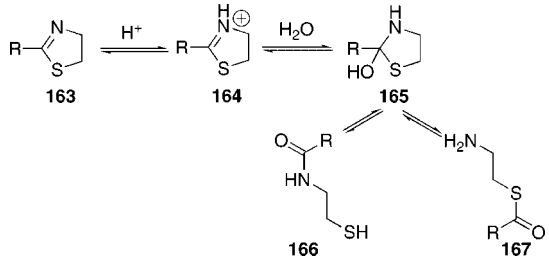
Formation of thiazoline **168** followed by its transformation into 4-methyl thiazoline **169** and subsequent ring opening was used as a protection−deprotection sequence for conversion of L-cysteine **1a** into its homologue 2-methyl cysteine **6a**. Both enantiomers could be obtained upon HPLC separation of 4-methyl thiazoline **170** (Scheme 57).[10]

Ring opening of 4-cyclopropyl-substituted thiazoline **171** by water hydrolysis afforded the corresponding *N*-acyl-2-amino thiol **172**, while acidic hydrolysis afforded the expected 2-amino thiol **173** (Scheme 58).[54]

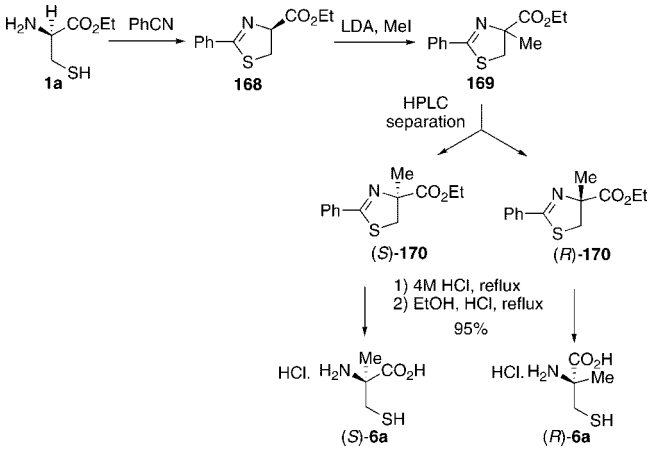
The thiazoline ring was also used in **174** as a protective group for 2-amino-2-deoxy-3-thio-mannose.[76] The authors reported the remarkable resistance of the thiazoline ring to strong acids and achieved cleavage using aqueous trifluoroacetic acid at room temperature to obtain the acetamido−thiol compound **175** (Scheme 59).[59]

Thiazolines **176** can be alkylated in the 4 position under asymmetric phase-transfer catalysis (PTC) conditions with alkyl, allyl, propargyl, and benzyl halides. When alkylation of **176a** and **176b** was performed in the presence of a chiral PTC catalyst (cat*1 or cat*2), thiazolines **177a** and **177b** were, respectively, obtained with high enantioselectivities and then transformed by acidic hydrolysis into the corresponding enantiomeric alkylcysteines (*R*)-**178** and (*S*)-**178** (Scheme 60).[77]

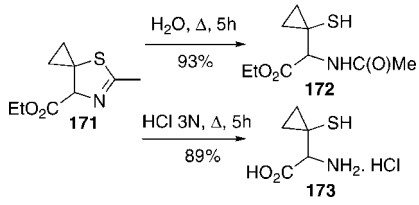
Scheme 56



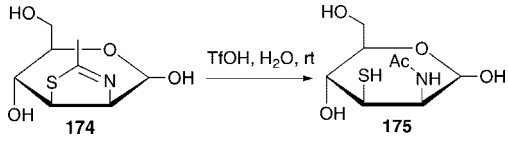
Scheme 57



Scheme 58



Scheme 59



3.4. Synthesis and Applications of α,β-Unsaturated Thiazolines

α,β-Unsaturated thiazolines are generally obtained by Horner−Wadsworth−Emmons reaction from α-phosphorylated alkylthiazolines or reactions of α-deprotonated 2-methyl-2-thiazoline with C═O electrophiles. They are useful intermediates, in particular, in the synthesis of biomolecules. Moreover, when chiral they are interesting reagents for asymmetric syntheses, as, for example, Michael acceptors or heterodienes partners in cycloaddition reactions.

Thiazolines substituted in the α position by a phosphoryl group can be used as Horner−Wadsworth−Emmons (HWE) reagents to introduce the thiazoline moiety in the structure of various compounds in particular of biological interest.[2a,b,3a,65c,52,78] As an example, arylvinylthiazolines **180** with potential antifungal activity have been prepared in low to moderate yields by HWE reaction between thiazoline−phosphonate **78a** and aromatic aldehydes **179** using sodium hydride as a base and THF as solvent in the deprotonation step (Scheme 61).[79]

In the synthesis of thiangazole the intermediate *E*-cinnamylthiazoline **182** was obtained in good yield from phosphine oxide thiazoline **181** and benzaldehyde using DBU as a base in the presence of LiCl in acetonitrile (Scheme 62).[10]

The DBU/LiCl/CH_3CN system was also successfully used to prepare α,β-unsaturated thiazolines from thiazoline−phosphonates used as chiral HWE reagents and aldehydes or ketones.[48a] As an example, starting from thiazoline−phosphonate **78b** and carbonyl derivative**183**, α,β-unsaturated thiazolines **184** were prepared (Scheme 63).[48a] Upon reacting **78b** with D-mannofuranose the α,β-unsaturated intermediate resulting from the HWE reaction underwent an intramolecular Michael addition, leading in low yield to product **185** as a mixture of α and β anomers.[48d]

Various α-fluoro-α,β-unsaturated thiazolines **187**, which are precursors of new modified peptides, have been prepared starting from α-fluoro-α-phosphonothiazolines **186** as original HWE reagents (Scheme 64). A mixture of *E*/*Z* isomers was obtained whatever the substituents with moderate to good selectivity in favor of the *E* isomer (*E*/*Z* = 65/35 to 95/5).[80]

Alkenylthiazolines were also used as azadienes in hetero-Diels−Alder reactions. In the first example, achiral alkenylthiazoline **188** was used as azadiene in reaction with diphenylketene **189**, leading to racemic cycloadduct **190** (Scheme 65).[81]

An asymmetric version of this aza-Diels−Alder reaction was then reported using chiral α,β-unsaturated thiazolines.[82] Enantiopure *E*-cinnamylthiazolines **191** were prepared by an alternative procedure of the HWE-type reaction starting from 2-methyl-2-thiazolines by deprotonation with LDA, reaction with benzaldehyde, and water elimination promoted by trifluoroacetic acid. Reaction of thiazolines **191** with 2 equiv of diphenylketene or tosyl isocyanate led stereoselectively to a single cycloadduct **192** or **193**, respectively (Scheme 66). Two heterocumulenes could be incorporated into the product in a controlled manner: the first one reacted as a dienophile, and the second one reacted with the electron-rich double bond of the formed adduct. The mixed double-addition product **194** was obtained when two different heterocumulenes (diphenylketene and tosyl isocyanate) were used.

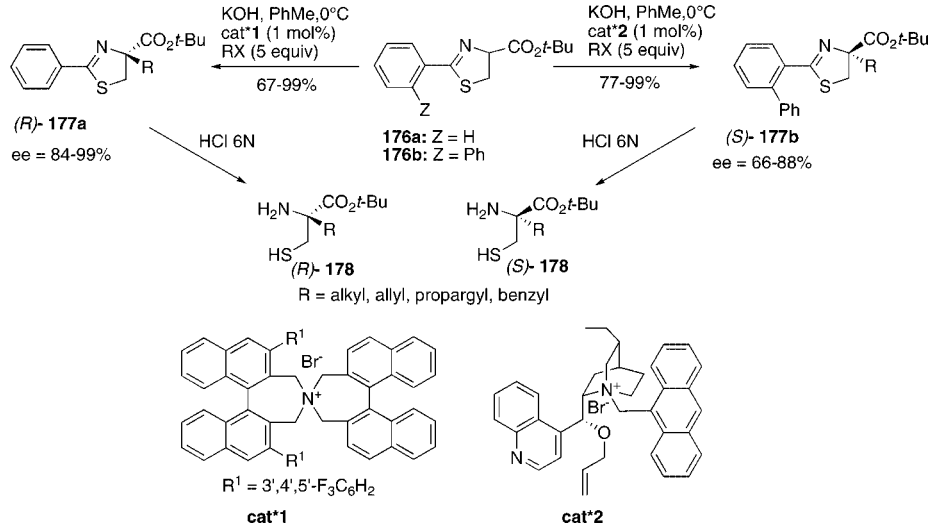
α,β-Unsaturated thiazolines **195** were used as Michael acceptors in the reaction with thiophenol as sulfur nucleophile. A catalytic amount of triethylamine was necessary to promote the reaction. Adducts **196** were obtained quantitatively as a mixture of two diastereomers in a 1/1 ratio. To avoid formation of diastereomeric mixtures, prenylthiazolines **197** were used leading to β-phenylsulfanyl thiazolines **198** (Scheme 67).[83]

3.5. Synthesis of Thiazolinium Salts

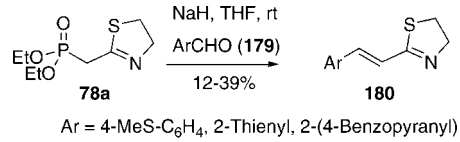
Another important application of thiazolines is their transformation into thiazolinium salts. These salts are encountered in various cyanine dyes,[84] photochromatic compounds,[85] and DNA markers for diagnosis in medicine.[86] Some of them have also demonstrated some antitumor properties.[87] Recently they aroused the attention of chemists because of their interesting properties as new chiral ionic liquids.[88]

The thiazolinium salts **200** were simply prepared by *N*-alkylation of the corresponding thiazolines **199** (Scheme 68, Table 7) under moisture-free conditions.[89,90] The most

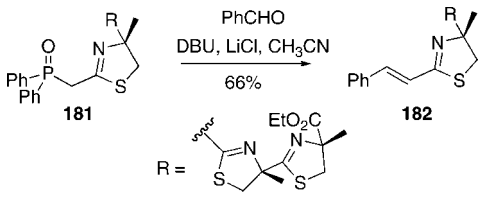
Scheme 60



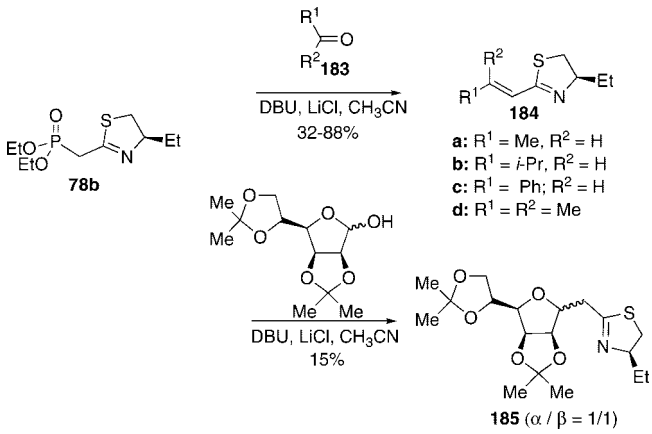
Scheme 61



Scheme 62

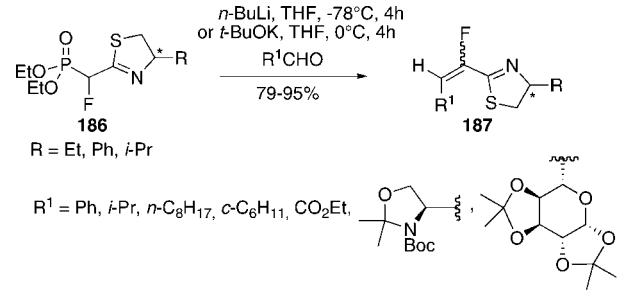


Scheme 63

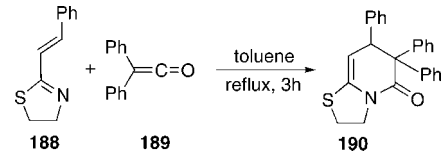


useful alkylating agents are those having an excellent leaving group (iodide and *p*-toluenesulfonate derivatives).[89−93] With less reactive nucleophiles such as bromide, lower yields are obtained (entries 21 and 22). Low molecular weight alkyl halides such as methyl iodide afforded good yields (Table 7, entries 1−16). However, branched chains (secondary alkyl halides) afforded in general lower yields or side products. As an example, reaction with 2-iodopropane afforded exclusively the protonated salt instead of the expected alkylated one (Table 7, entry 17). With 2-methyl-thiazoline care has to be taken to avoid formation of cyanine-type

Scheme 64



Scheme 65

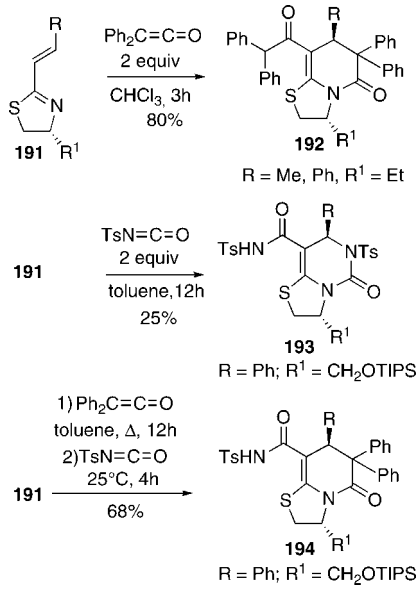


compounds.[90] Substitution by bulky groups on the 2 position of thiazolines also resulted in lower alkylation yield (Table 7, entry 6). Functionalized thiazolinium salts having a carboxylic ester function were also prepared by this procedure.[91] Alkylsulfonate electrophiles proved to be efficient, especially when the alkylation was done in chlorobenzene as the solvent (Table 7, entries 23−27).[93,94]

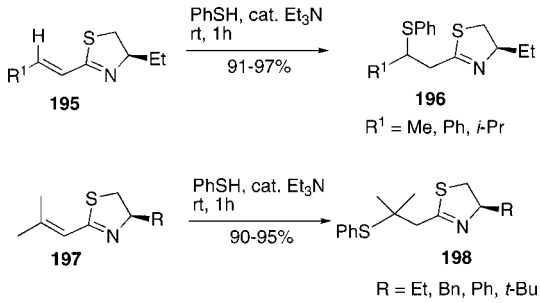
Chiral thiazolinium salts, having the chirality on the carbon α to the nitrogen atom, were also prepared similarly from chiral thiazoline precursors (Scheme 69, Table 8).[91,88a] Alkylation with methyl iodide is efficient (Table 8, entry 1), while alkylation using ethyl iodide is more sluggish (Table 8, entry 2). The halide counterion of thiazolinium salts **202** can be exchanged using $LiNTf_2$, $NaPF_6$, and $NaBF_4$ (or the corresponding acids), affording new salts **203**, which have, for most of them, ionic liquid properties.[88]

In one example, a zwitterionic salt was obtained by reaction between chromate complex **204** and thiazoline **129** (Scheme 70).[95] This compound was obtained as a mixture with the substitution complex **206**. The given yield relative to $Cr(CO)_6$ complex are rather low (11%). The structure of the zwitterion **205** was confirmed by an X-ray structural analysis.

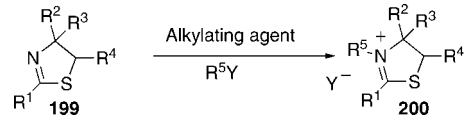
Scheme 66



Scheme 67



Scheme 68



3.6. Miscellaneous

3.6.1. Reactions with C═N Electrophiles

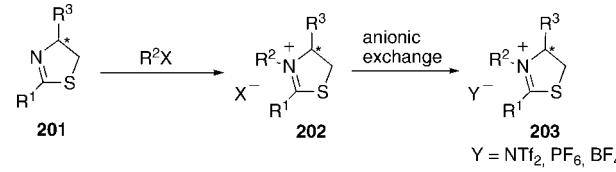
Deprotonation of 2-alkyl thiazolines in the α position using LDA or BuLi followed by reaction with C═N electrophiles such as nitriles and imidoyl chlorides afforded masked *β*-enamino acid derivatives. Treatment at low temperature of 2-methyl-2-thiazoline **129** with LDA followed by subsequent reaction with nitriles **207** afforded imines **208** or the corresponding enamines **209**, which are in tautomeric equilibrium. In the reaction depicted in Scheme 71, only product **209** was obtained after quenching with saturated aqueous NH_4Cl solution.[96] When imidoylbenzotriazoles **210** served as electrophiles, enamines thiazolines **211** were obtained in good yields (Scheme 71).[97]

Upon deprotonation of 2-methyl-2-thiazoline **129** in the α position using LDA and subsequent reaction with different aromatic or aliphatic dielectrophiles various heterocycles such as 3-aminoindene **213**, phtalimidine **214**, and pyrrolidine **215** were obtained in an elegant addition−cyclization reaction (Scheme 72).[98]

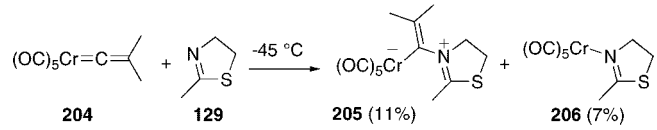
Table 7. Thiazolinium Salts 200 Prepared by Alkylation of Thiazolines 199 (selected examples)

entry	R^1	R^2	R^3	R^4	R^5	Y	yield (%)	ref
1	Me	H	H	H	Me	I	100	89
2	Et	H	H	H	Me	I	80	89
3	Pr	H	H	H	Me	I	80	89
4	*i*-PrCH_2	H	H	H	Me	I	80	89
5	*i*-PrCH_2	H	H	*t*-Bu	Me	I	90	89
6	*t*-BuCH_2	H	H	*t*-Bu	Me	I	40	89
7	PhCH_2	H	H	H	Me	I	100	89
8	PhCH_2	Me	H	Me-cis	Me	I	100	89
9	PhCH_2	Me	H	Me-trans	Me	I	100	89
10	CH_2OMe	H	H	H	Me	I	90	89
11	CH_2OMe	Me	Me	H	Me	I	55	89
12	CH_2OMe	H	H	Me	Me	I	100	89
13	CH_2OMe	H	H	Me	*i*-Pr	I	63	89
14	CH_2OEt	Me	Me	H	Me	I	100	89
15	CH_2OPr	Me	Me	H	Me	I	100	89
16	CH_2O-*i*-Pr	Me	Me	H	Me	I	100	89
17	CH_2O-*i*-Pr	Me	Me	H	*i*-Pr	I	100	89
18	CH_2OBu	Me	Me	H	Me	I	70	89
19	CH_2OPh	H	H	H	Me	I	72	89
20	CH_2OPh	Me	Me	H	Me	I	60	89
21	Me	H	H	H	PhCH_2	Br	63	90
22	Ph	H	H	H	PhCH_2	Br	45	90
23	Me	H	H	H	Et	$EtOSO_3$	82	94
24	Me	H	H	H	$CH_3(CH_2)_6$	OTos	54	93
25	Me	H	H	H	$CH_3(CH_2)_7$	OTos	62	93
26	Me	H	H	H	$CH_3(CH_2)_9$	OTos	62	93
27	Me	H	H	H	PhCH_2CH_2	OTos	53	93

Scheme 69



Scheme 70



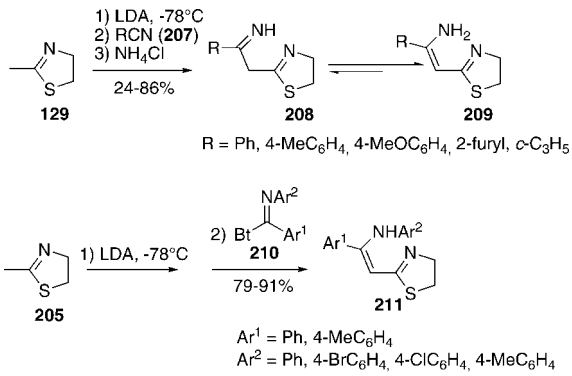
3.6.2. Ketene−Imine Cycloadditions

2-Alkyl-2-thiazolines **216** reacted with Meldrum's acid derivative **217** in 1,2-dichloroethane to afford ring-fused 2-pyridinones **218**(Scheme 73).[99]

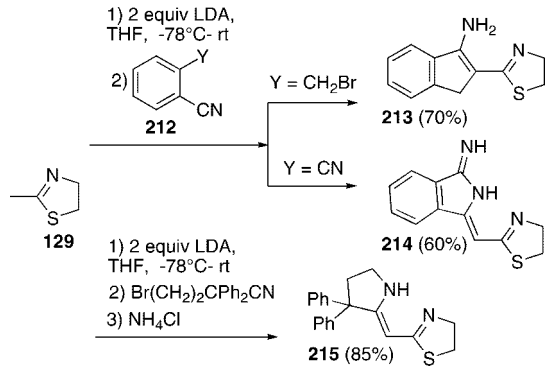
3.6.3. Reactions in the Ortho Position of 2-Aryl-Thiazolines

Compared to 2-aryl-oxazolines, which are widely used for synthetic applications as substrates in aromatic nucleophilic substitutions, nucleophilic additions, metalation, and electrophilic substitutions on the aromatic ring,[2b] 2-aryl-thiazolines are only poorly studied and used for this purpose. Only one example of nucleophilic substitution at the aromatic moiety was reported. 2-Fluoro-phenylthiazoline **219** reacted with potassium diphenylphosphide to afford phosphine−thiazoline ligand **L12** (see section 5),[48e] which is the sulfur analogue of the well-known Pfaltz's phosphine−oxazoline ligand (Scheme 74).

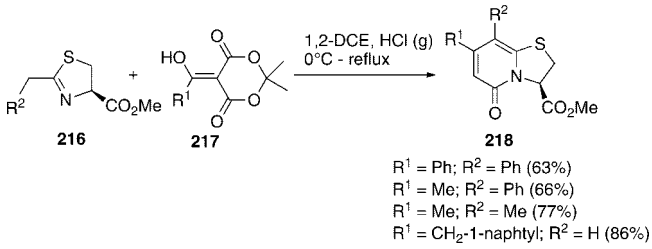
Scheme 71



Scheme 72



Scheme 73



3.6.4. Reactions Involving Functional Groups on the Thiazoline Ring

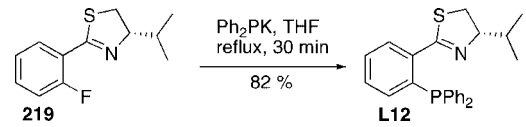
The reactivity of the thiocarbonyl group in thiazoline-5-thiones **220** was explored in various reactions including 1,3-dipolar cycloadditions, Diels−Alder reactions, ring expansion of oxiranes, and C-alkenylation followed by radical cyclizations (Scheme 75).[100] The resulting products **221**, **222**, **223**, and **224** are spirocyclic sulfur heterocycles with interesting structures.

(*Z*)-2-Substituted-4-benzylidene-5-(4*H*)-thiazolone **225** reacted with diazomethane, affording different products depending on the reaction conditions: in benzene at 45 °C cyclopropanethiazolone **226** was mainly obtained, whereas in ether at 0 °C a ring expansion took place together with epoxidation leading to product **227** (Scheme 76).[101]

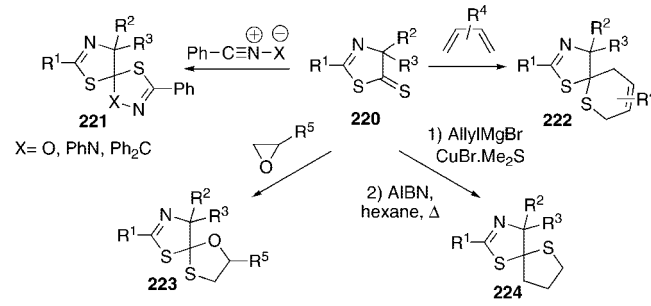
4. Thiazoline Compounds of Biological Importance

The thiazoline ring is present in many biologically active compounds, including natural[102] and synthetic products. Some thiazoline-containing compounds have pharmacological properties, acting as antibiotic, anticancer, or anti-HIV agents. Others have antihelmintic or antifungal activities. Lastly, some thiazolines with a small molecular mass have found applications in food and flavor chemistry.[103] There is a large number of publications dealing with the structural and biological studies of thiazoline-based compounds. Since these aspects are beyond the scope of the review, we selected in this section publications related to the synthetic aspects and the biological properties of these thiazoline derivatives of biological importance.

Scheme 74



Scheme 75



4.1. Natural Products

4.1.1. Thiazoline-Containing Polyazoles

The presence of multiple directly linked heterocycles (thiazoline, thiazole, oxazole) is a structural feature of a class of natural alkaloids including tantazoles, mirabazoles, and thiangazole (Figure 4).

Mirabazoles and tantazoles were isolated from blue-green algae *Scytonemea mirabile* and are studied for their cytotoxic and anticancer properties.[104] Thiangazole was isolated from a metabolyte of *Polyangium spec.* strain P13007 and studied for its antihelmintic and antiviral properties.[105,106] Due to their unusual polyazole structure but also to their biological properties, these compound have aroused great interest for organic chemists. Most of these compounds have been the target for total synthesis. More than one thiazoline ring (2, 3, or 4) derived from 2-methylcysteine is contained in these compounds. In most of cases,

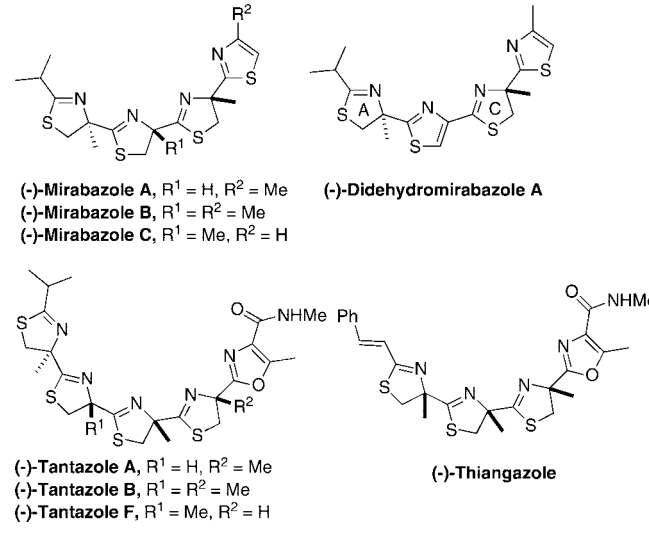
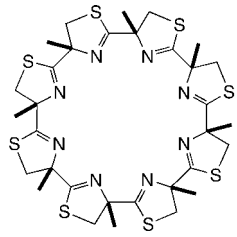
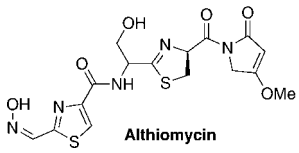


Figure 4.

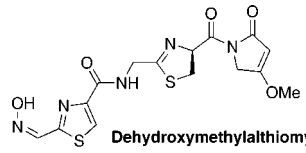


24-Membered cyclic oligothiazoline

Figure 5.



Althiomycin



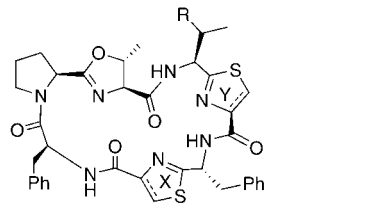
Dehydroxymethylalthiomycin

Figure 6.

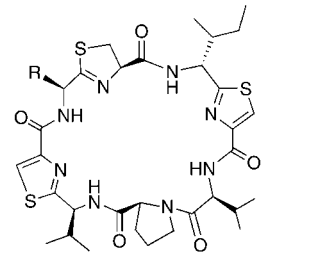
the starting sulfur-containing precursor used for thiazoline ring formation is the 2-methylcysteine, which is available from the chiral pool as the (*R*) or (*S*) enantiomer (from L-cysteine[7,10,107] or from D-alanine[22a]) with a free or protected thiol function. Starting from *S*-benzyl protected (*R*)-2-methylcysteine, thiazoline rings belonging to (−)-mirabazole B,[108] (−)-mirabazole C,[109] and (−)-thiangazole[10,22a,b] were formed using the $TiCl_4$-mediated cyclization (see section 2.1, Schemes 17 and 18). The thiazoline rings from (−)-thiangazole were synthesized from (*R*)-2-methylcysteine and nitriles (see section 2.1).[7] The method using amino thiols and iminoethers for thiazoline ring formation (see section 2.1) was applied in the synthesis of natural (−)-didehydromirabazole A, which has a *R* configuration on the chiral carbon atom in ring **A** and *S* in ring **C** (Figure 4). To prepare the thiazoline rings the authors used subsequently (*R*)- and (*S*)-2-methylcysteine.[110] For the unnatural (*R*)-isomer (*S*-configuration in **A** and **C** rings), only (*R*)-methylcysteine was used.[111] Thioacids were also used as sulfur precursors in some syntheses. As an example, thioisobutyric acid was used in the formation of the thiazoline rings in (−)-tantazole[58] (see section 2.3) and thioacetic acid in the (−)- and (+)-thiangazole syntheses.[78e,112] This methodology was used in an iterative thiazoline formation sequence, which ended by a head-to-tail cyclooligomerization, enabling the synthesis of an original family of 24- to 36-membered cyclic oligothiazolines, as represented in Figure 5.[113] The authors showed that macrocycles of this type have applications in the area of molecular or ion recognition (strong binding affinity to heavy metal ions such as Pb^{3+} and Cd^{3+} [114] or selective interactions with small chiral molecules, i.e., mandelic acid).[115]

4.1.2. Thiazoline-Containing Linear Peptides

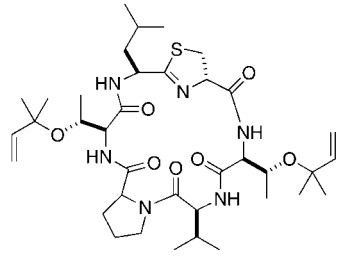
Althiomycin (Figure 6) is a thiazoline-containing antibiotic, which was isolated in 1957 from *Streptomyces althioticus*.[116] Its biological action is believed to arise from its ability to inhibit protein synthesis at the peptidyltransferase stage.[117] In the total synthesis of althiomycin, thiazoline ring



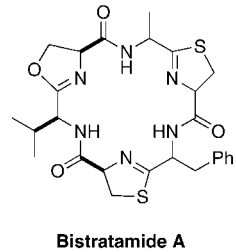
Lissoclinamide-3 (R = Me, X: thiazole, Y: thiazoline)
Lissoclinamide-4 (R = H, X: thiazole, Y: thiazoline)
Lissoclinamide-7 (R = H, X: thiazoline, Y: thiazoline)



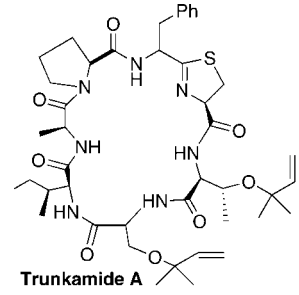
Tawicyclamide A : R = CH_2Ph
Tawicyclamide B : R = $CH_2CH(CH_3)_2$



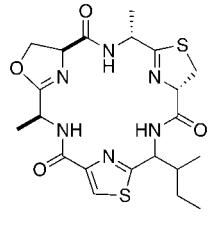
Patellin-2



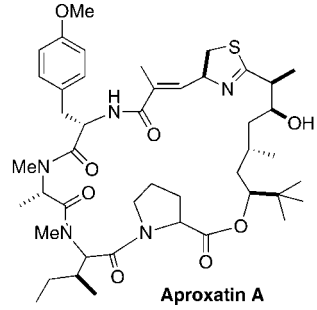
Bistratamide A



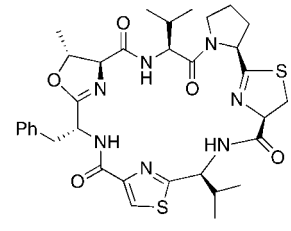
Trunkamide A



Dolastatin E



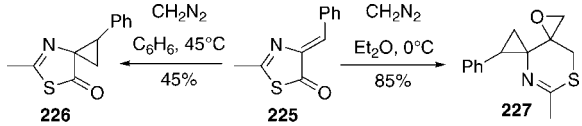
Aproxatin A



Cyclodidemnamide

Figure 7.

Scheme 76



was formed in a modest yield (40%) from a *N*-(β-hydroxy)-amide precursor by reaction with Lawesson reagent in refluxing xylene.[118]

Analogues of althiomycin were also reported,[119,120] but their antimicrobial activities were not systematically evaluated. Both total synthesis and semisynthetic methodologies have been used by Zarantonello et al. for the synthesis of almost 50 analogues. In these syntheses the thiazoline ring was formed using an activated thioacyl species, the [2-(6-nitrobenzotriazol-1-yl)-2-thioxoethyl]-carbamic acid *tert*-butylester. Only one of the tested analogues, the dehydroxymethylalthiomycin (Figure 6), showed appreciable antibacterial activity against a panel of Gram-positive and Gram-negative bacteria (minimum inhibitory concentration (MIC) < 32 μg/mL). However, the antibacterial activity was lower than that of althiomycin (1< MIC <16 μg/mL).

4.1.3. Thiazoline-Containing Cyclopeptides

Thiazolines are structural segments of various cyclopeptide alkaloids,[102b,d] which were extracted from different marine organisms. Lissoclinamides[121,122] patellins,[123] tawicyclamides,[124] bistratamides,[125] and trunkamides,[126] which were extracted from *Lissoclinum patella*, dolastatin E,[127] isolated from the see hare *Dolabella auricularia*,[128] or apratoxins isolated from *Lyngbya majuscula*[129] (Figure 7). Among the different structures of lissoclinamides, the lissoclinamide 7 having two thiazoline rings was found to be the most cytotoxic when tested with human fibroblast, bladder carcinoma cell lines, and normal lymphocytes (IC_{50} < 0.1 μg/mL).[122] Trunkamide A was reported to have promising antitumor activity.[130] For the preparation of these natural cyclic peptides, different methods were used for thiazoline ring formation. Cysteine ester and N-protected iminoethers were used for lissoclinamides.[15] In the synthesis of trunkamide A,[131] *N*-(β-hydroxy)amides were reacted with Lawesson's reagent followed by subsequent cyclization using DAST reagent. For the cyclodidemnamide[51] the route involving thioacylation of amino alcohols using a benzotriazole proline thioamide derivative followed by cyclization with Burgess reagent was preferred.

Table 8. Enantiopure Thiazolinium Salts 202 Prepared by Alkylation

entry	R^1	R^2	R^3	X	conditions	yield (%)	ref
1	Me	Me	CO_2Me	I	reflux, 1 h	84	91
2	Me	Et	CO_2Me	I	reflux, 24 h	63	91
3	*i*-Pr	Bu	Et	I	reflux, 2 days	66	88a,b
4	*i*-Pr	Dod	Et	I	reflux, 2 days	30	88a,b
5	*i*-Pr	Dod	Bn	I	100 °C, 7 days	24	88a
6	*i*-Pr	Bu	Bn	I	70 °C, 2 days	64	88a,c
7	*i*-Pr	Et	Bn	I	70 °C, 2 days	66	88a

Thiostrepton (Figure 8) was isolated from the culture broth of Streptomyces azureus. It belongs to a family of peptide antibiotics[132] whose mode of action involves RNA binding. Its structure is highly complex with two macrocycles and a thiazoline moiety, which makes the structural particularity of thiostrepton, when compared to other peptide antibiotics of the same family, which have a thiazole instead of the thiazoline ring. The total synthesis of thiostrepton and some analogs was described by Nicolaou et al.[133] The thiazoline moiety was built from a dipeptide obtained from threonine and serine and thionation with Lawesson's reagent followed by cyclization of the *N*-(β-hydroxy)thioamide intermediate using DAST.[133a] A thiazoline-containing segment of thiostrepton was also synthesized separately,[134] and the oxazoline−thiazoline transformation was performed in two steps using oxazoline sulfhydrolysis and subsequent *N*-(β-hydroxy)-thioamide cyclization with DAST. Siomycin A (Figure 8), which has a structure similar to that of thiostrepton, was isolated from *Streptomyces sioyaensis*[135] and targeted for a total synthesis.[136]

Bacitracin A belongs to a family of dodecapeptide antibiotics, which is produced nonribosomally by *Bacillus subtilis* and licheniformis.[137] In contrast to the other thiazoline-containing cyclopeptides, the thiazoline moiety is not part of the macrocycle but is part of a lateral peptidic linear chain (Figure 9). Bacitracin derivatives were described to exhibit a receptor-like mode of action; in conjunction with a divalent metal ion, they bind to and sequester bactoprenyl pyrophosphate, which is involved in cell wall biosynthesis. Bacitracin is widely used as a component of topical antibacterial ointments and as an additive in animal feeds. It was also found to eradicate intestinal colonization by vancomycin-resistant *Enterococcus faecium*.[138] Griffin et al. reported a solid-phase method for the total synthesis of bacitracin A in which the thiazoline moiety was obtained from methylcysteine methyl ester and the iminoether derived from isoleucine.[138]

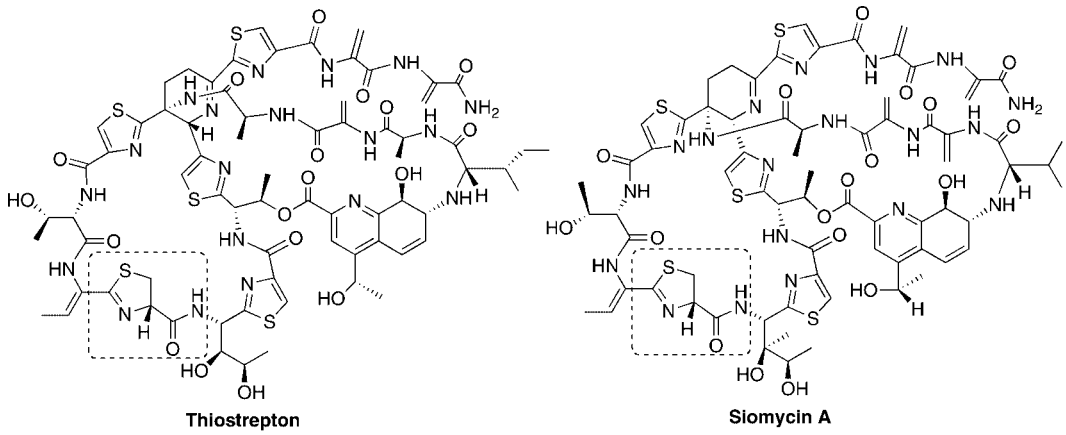


Figure 8.

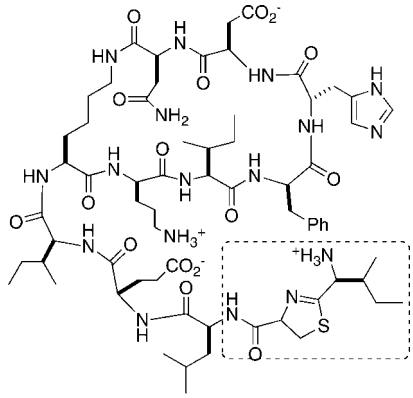


Figure 9.

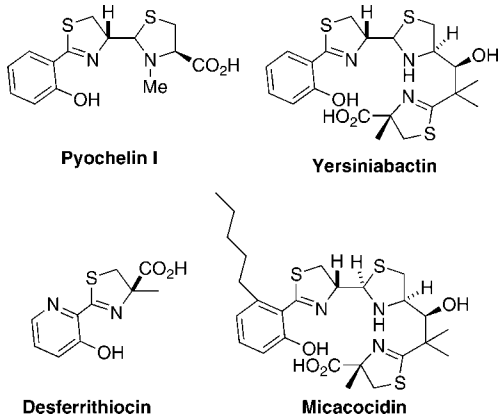


Figure 10.

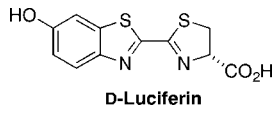


Figure 11.

4.1.4. Hydroxy Aromatic and Heteroaromatic Thiazolines

Siderophores such as pyochelin,[139] yersiniabactin,[140] and desferrithiocin[141] are compounds containing a phenol or hydroxypyridyl moiety which is substituted in the ortho position by a thiazoline ring (Figure 10). They are produced by microorganisms (pyochelin has been isolated from *Pseudomonas aeruginosa*, yersiniabactin from *Yersinia enterocolitica*, and desferrithiocin from *Streptomyces antibioticus* DSM 1865) and enhance microbial growth by binding ferric iron and accelerating its transport. Pyochelin is presumed to be biosynthesized from salicylic acid and two molecules of cysteine. It exists in nature as a mixture of two interconvertible isomers. Bergeron et al. studied the structure−activity relationship for desferrithiocin by evaluation of a series of synthetic analogues as orally effective iron chelators. The results showed that the aromatic hydroxyl and carboxyl are important functions for ligand activity, while the pyridine is of little importance. Micacocidin, which was isolated from the culture broth of Pseudomonas sp. No. 57−250, is an antibiotic having specific and potent antimycoplasma activity.[142,143] Due to their biological properties, these compounds (and their metal complexes with Zn^{2+}, Cu^{2+}, and Fe^{3+}) have received considerable attention as targets for total synthesis. The thiazoline ring was formed in different ways, for example, by condensation of the salicylic nitrile with L-cysteine for pyochelin.[139a,141] For yersiniabactin, the thiazoline ring resulted from a *N*-(*β*-hydroxy)thioamide intermediate by cyclization using Burgess reagent.[36] For micacocidin, cyclization of the S-protected cysteine derivative was promoted by either phosphorus pentachloride or trifluoroacetic acid.[142−144]

Firefly luciferin (D-luciferin), which is a light-emitting pigment, contains both a hydroxybenzothiazole and a thiazoline in its structure (Figure 11).[145] It was chemically synthesized from 2-cyano-6-hydroxybenzothiazole and D-cysteine.[145a] A recent study dealing with the biosynthetic pathway of D-luciferin showed a possible conversion of L-cysteine via L-luciferin into D-luciferin.[146] Although this molecule has no pharmacological properties, its bioluminescence property was recently used in the medical field as a positive test to control release of a drug from a luciferin-transporter drug system.[147]

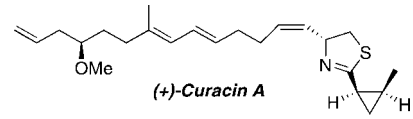


Figure 12.

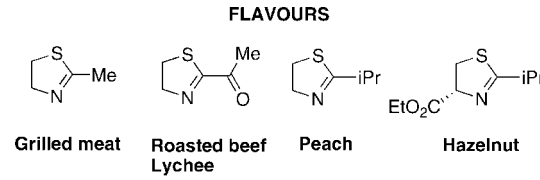


Figure 13.

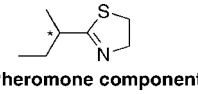


Figure 14.

4.1.5. Other Structures

(+)-Curacin A (Figure 12) is a lipidic agent isolated from the cyanobacterium *Lyngbya majuscula*, which was found to be a potent antimitotic agent (IC_{50} = 2−200 nM in three cell lines). It is highly toxic to brine shrimp (LC_{50} = 25 ng/mL), which exhibits mammalian cell antiproliferative activity. Curacin A acts as an inhibitor of tubulin polymerization by interaction with the colchicine binding site on tubulin.[78c,148] The total synthesis of curacin A has attracted significant attention. Different methods for thiazoline ring formation were used: (i) cyclization in refluxing benzene of an amino thioester, (ii) cyclization of a *N*-(*β*-hydroxy)thioamide intermediate, (iii) thioacylation of an aminoalcohol with a benzotriazole derived from a cyclopropyl thioamide followed by cyclization with Burgess reagent (see section 2.2.2, Scheme 36),[52] and (iv) sulfhydrolysis of oxazoline−cyclopropane derivatives.[149−151] It is worth noting that the alkenyl thiazoline moiety is responsible for the chemical instability of the natural product. Some analogues of curacin A were synthesized for a structure−activity relationship study. Replacement of the thiazoline or of the cyclopropyl moiety by other heterocycles afforded less active compounds.[152]

4.1.6. Thiazoline-Containing Aroma and Flavors

Some small molecules containing the thiazoline heterocycle belong to a class of volatile aroma found in vegetables, cooked meat, and other processed foods[103] (Figure 13). Food

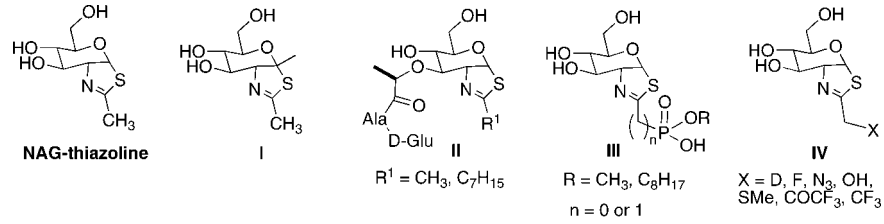


Figure 15.

systems (meat) containing cysteine or cystine are known to develop sulfur-containing flavors after roasting. As an example, 2-acetyl-2-thiazoline is a well-known odor-active compound which was detected as a component of the roasted-meat flavor[103a] or of the lychee fruit.[153] A few synthetical routes have been described for its preparation: by condensation of cysteamine with nitrile derivatives[154] and by Ru-catalyzed oxidation of 2-acetyl-2-thiazolidine obtained from cysteamine and 2-oxopropanal (see section 2.1).[20] Different analogues of 2-acetyl-2-thiazoline have been synthesized and shown to exhibit interesting flavors for the food industry.[103c,155,156]

The 2-*s*-butyl-2-thiazoline is a pheromone component which was isolated from mice's urine *Mus musculus* (Figure 14).[157] Both enantiomers have been synthesized and characterized.[158] The stereochemical integrity was found to be very sensitive to the reaction conditions. The authors obtained the best result (92% ee) upon reacting enantiopure 2-methylbutanoic methyl ester with cysteamine in the presence of triisobutylaluminium in refluxing toluene.

4.2. Synthetic Products

NAG-thiazoline (Figure 15) was found to be a potent competitive inhibitor (K_m = 0.62 mM) of jack bean *N*-acetylhexosaminidase, an enzyme that promotes cleavage of *N*-acetylhexosaminidines during glycoprotein and glycolipid catabolism.[159,160] The thiazoline ring of NAG-thiazoline was first prepared by thionation with Lawesson's reagent of the commercial 2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (glucosamine pentaacetate) followed by cyclization using displacement of an acetate.[159] The NAG-thiazoline triacetate is now widely used and produced in a multigram scale by treatment of glucosamine pentaacetate with P_4S_{10}.[161] Several analogues (Figure 15) have been synthesized to improve the selectivity of the NAG-thiazoline inhibition. For example, NAG-thiazoline was functionalized with a peptide chain (structure **II**)[40a] and a phosphonate moiety (structures **III**)[40a] or modified via an enamine intermediate to which a "X" substituent was introduced via electrophilic or radical addition (structures **IV**).[162] Two of these analogues, the azide (**IV**, X = N_3) and the fluoride derivatives (**IV**, X = F), exhibit excellent selectivity for *O*-GlcNAcase and inhibitory activity.

A series of 2-aryl thiazolines (Figure 16) has been synthesized and tested as *Pseudomonas aeruginosa* deacetylase LpxC inhibitors.[163] The method used for formation of the thiazoline cycles involves sulfhydrolysis of oxazolines followed by cyclization using DAST. These thiazolines were selected for a theoretical study in order to correlate their structure and electronic properties (electrostatic potential surfaces) with their biological activity.[164]

The thiazoline derivative illustrated in Figure 17 was studied as a conformationally restricted benzamide bioisostere, which is known for selective dopamine D4 receptor binding.[165] This compound was synthesized in four steps starting from the unnatural (*S*)-cysteine ethyl ester or in six steps starting from serine methyl ester via oxazoline sulfhydrolysis. The tests in vitro showed that the thiazoline has a moderate affinity in radioligand binding.

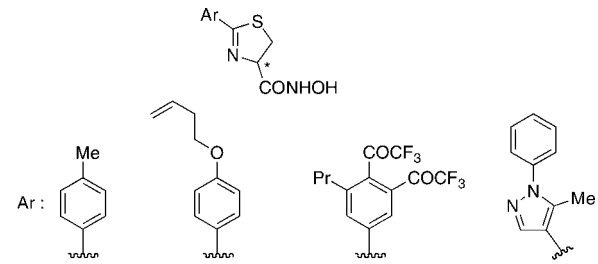


Figure 16.

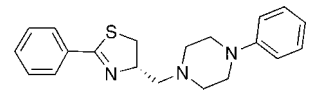
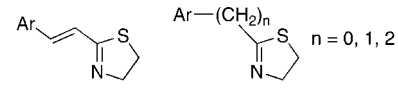


Figure 17.



Ar = Ph, p-Tolyl, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 1- or 2-napthyl...

Figure 18.

A series of 27 aryl−alkyl and aryl−vinyl thiazolines (Figure 18) was synthesized and tested for antihelmintic and antifungal activities.[79] The structure−activity relationship study showed that the nature of the substituent in the 2 position of the thiazoline moiety is essential for the activity. For example, high antihelmintic activity was found for the derivatives having a vinyl or naphthyl substituent. The arylvinylthiazolines have been found to have interesting filaricidal activity against *Molinema dessetae* with a nematicidal activity of 4 < CE_{50} < 26 μg/mL (active reference Tetramisole, CE_{50} = 70 μg/mL) and antifungal activity against *Scopulariopsis brevicaulis* yeast of 6 < CMI < 78 μg/mL (active reference Econazole, CMI = 64 μg/mL). In all examples the thiazoline cycle was formed by condensing cysteamine with the corresponding nitrile in refluxing ethanol.

5. Chiral 2-Thiazolines as Ligands for Asymmetric Catalysis

The preparation of new enantiopure ligands that provide a chiral environment to transition metals is still a challenging topic for chemists. Due to the high efficiency of oxazolines in asymmetric catalysis it is not surprising that the corresponding sulfur analogues were evaluated as ligands. However, in comparison to their oxygen counterparts, the thiazolines have been poorly used in catalysis. The main derivatives, which were synthesized as ligands, are given in Figure 19.[42,43,47,48c,e,166−172] Most of them are analogues of the well-known oxazolines. It is worth noting that thiazolines

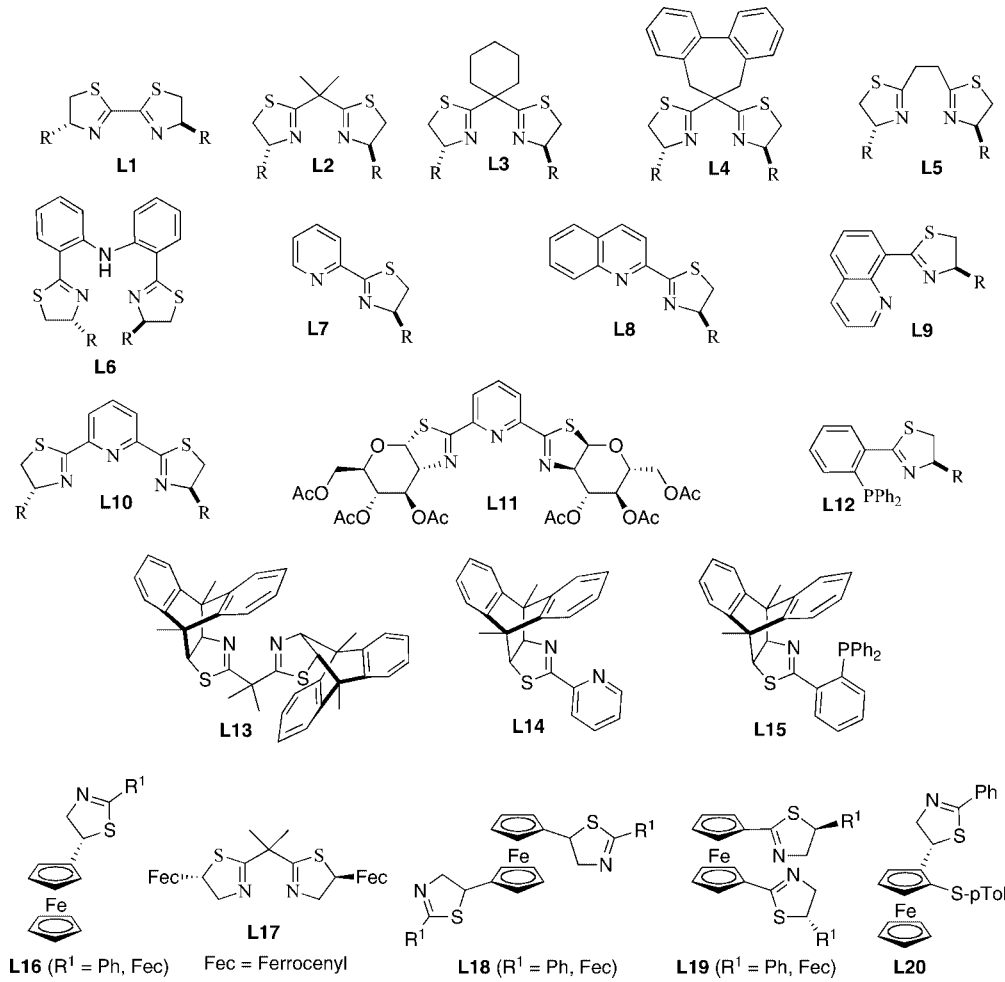
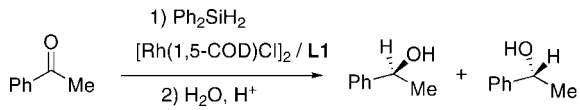


Figure 19. Thiazolines ligands: **L1**,[47] **L2** and **L3**,[48c,e] **L4**,[42] **L5**,[170] **L6**,[43,169] **L7**−**L9**,[48c,e] **L10**,[48c,e,166] **L11**,[172] **L12**,[48e] **L13**−**L15**,[167] **L16**−**L19**,[171a,b] and **L20**[171c] (relative configurations are given for general structures with the R substituent).

Scheme 77



have been recently mentioned in two reviews devoted to sulfur-containing ligands.[173]

The first study using thiazolines as ligands was reported by Helmchen in 1991. He studied the efficiency of C_2-symmetric bis(thiazolines) **L1** in the rhodium-catalyzed asymmetric hydrosilylation of acetophenone. However, the real interest in this new family of ligands only appeared at the beginning of the 21st century with the synthesis of various new thiazolines and study of their catalytic properties in various reactions such as palladium-catalyzed asymmetric allylic substitution, ruthenium-catalyzed cyclopropanation of alkenes, copper-catalyzed asymmetric Diels−Alder reaction, asymmetric Henry reaction, palladium-catalyzed C−P bond formation, zinc-catalyzed Michael addition of nitroalkanes to nitroalkenes, and zinc-catalyzed enantioselective Friedel−Crafts reactions.

5.1. Hydrosilylation

The rhodium-catalyzed hydrosilylation of acetophenone is a widely studied reaction. Satisfactory results were obtained with pyridyl oxazoline derivatives.[174] In 1991 Helmchen compared the performance of C_2-symmetric bis(thiazolines) and bis(oxazolines).[47] The reactions were carried out at rt with a 1.2:1 ratio of diphenylsilane to ketone and 0.5 mol % of [Rh(1,5-cyclooctadiene)Cl]$_2$. In all examples the (*S,S*) ligand afforded the *R* enantiomer of phenylethanol (Scheme 77, Table 9). With thiazolines **L1** the best level of enantioselection (50%) for a reasonable yield (72%) was obtained in toluene using the benzyl derivative (**L1e**). With the analogous oxazoline, CCl_4 was the solvent of choice, allowing a slightly higher ee (70%) but a lower yield (52%).

Table 9. Chiral Thiazoline Ligands in Rhodium-Catalyzed Hydrosilylation of Acetophenone[47]

entry	ligand (config)	R	*T*, solvent	ee (%) thia (oxa)[a]	product config thia (oxa)[a]	yield (%) thia (oxa)[a]
1	**L1b** (*S,S*)	*i*-Pr	rt, toluene	9 (1)	*R* (*R*)	68 (61)
2	**L1b** (*S,S*)	*i*-Pr	rt, CCl_4	3 (50)	*R* (*R*)	21 (nd)
3	**L1e** (*S,S*)	Bn	rt, toluene	50 (5)	*R* (*R*)	72 (48)
4	**L1e** (*S,S*)	Bn	rt, CCl_4	33 (70)	*R* (*R*)	nd (52)

[a] For comparison, the data for the corresponding oxazolines are given in parentheses.

Scheme 78

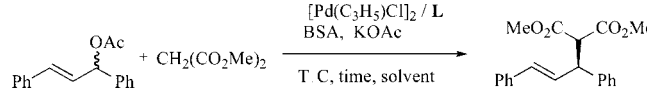


Table 10. Chiral Thiazoline Ligands in Pd-Catalyzed Allylic Substitution

entry	ligand L (config)	R	*T* (°C), time, solvent[a]	ee (%), thia (oxa)[b]	product config, thia (oxa)[b]	conv (%), thia (oxa)[b]	ref, thia (oxa)[c]
1	**L2a** (*R*,*R*)	Et	rt, 30 h, CH_2Cl_2	88 (4)	*R* (*R*)	95 (<10)	48e
2	**L2b** (*S*,*S*)	*i*-Pr	rt, 42 h, CH_2Cl_2	42 (19)	*S* (*S*)	95 (<10)	48e
3	**L2c** (*S*,*S*)	*t*-Bu	rt, 30 h, CH_2Cl_2	31 (33)	*R* (*S*)	90 (20)	48e
4	**L2e** (*S*,*S*)	Bn	rt, 72 h, CH_2Cl_2	70 (88)	*S* (*S*)	94 (97)	48e
5	**L3a** (*R*,*R*)	Et	rt, 48 h, CH_2Cl_2	51	*R*	95	48e
6	**L3b** (*R*,*R*)	*i*-Pr	rt, 72 h, CH_2Cl_2	41	*R*	95	48e
7	**L4b** (*S*,*S*)	*i*-Pr	0°, 72 h, CH_2Cl_2	56 (75)	*R* (*S*)[d]	89 (86)	42
8	**L4e** (*S*,*S*)	Bn	0°, 72 h, CH_2Cl_2	14 (73)	*S* (*S*)[d]	84 (83)	42
9	**L4f** (*S*,*S*)	*i*-Bu	0°, 72 h, CH_2Cl_2	16 (74)	*R* (*S*)[d]	87 (88)	42
10	**L4d** (*S*,*S*)	Ph	0°, 72 h, CH_2Cl_2	19 (86)	*R* (*S*)[d]	86 (90)	42
11	**L7a** (*R*)	Et	rt, 96 h, CH_2Cl_2	38	*R*	95	48e
12	**L7b** (*S*)	*i*-Pr	rt, 96 h, CH_2Cl_2	34 (24)	*S* (*S*)	95 (84)	48e (176)
13	**L7b** (*R*)	*i*-Pr	rt, 42 h, CH_2Cl_2	42	*R*	95	48e
14	**L7c** (*S*)	*t*-Bu	rt, 30 h, CH_2Cl_2	81	*S*	90	48e
15	**L7d** (*R*)	Ph	rt, 72 h, CH_2Cl_2	64 (55)	*R* (*R*)	94 (86)	48e (176)
16	**L8a** (*R*)	Et	rt, 144 h, CH_2Cl_2	59	*R*	95	48e
17	**L8b** (*S*)	*i*-Pr	rt, 144 h, CH_2Cl_2	65 (62)	*S*	95 (88)	48e (176)
18	**L8b** (*R*)	*i*-Pr	rt, 96 h, CH_2Cl_2	66	*R*	95	48e
19	**L8c** (*S*)	*t*-Bu	rt, 144 h, CH_2Cl_2	85 (92)	*S* (*S*)	70 (85)	48e (176)
20	**L8d** (*R*)	Ph	rt, 72 h, CH_2Cl_2	78 (68)	*R* (*R*)	53 (93)	48e (176)
21	**L9a** (*R*)	Et	rt, 240 h, CH_2Cl_2	13	*R*	19	48e
22	**L9b** (*S*)	*i*-Pr	rt, 240 h, CH_2Cl_2	21 (42)	*S* (*S*)	20 (96)	48e (176)
23	**L9c** (*S*)	*t*-Bu	rt, 240 h, CH_2Cl_2	22 (77)	*S* (*S*)	15 (88)	48e (176)
24	**L9d** (*R*)	Ph	rt, 240 h, CH_2Cl_2	48 (59)	*R* (*R*)	8 (94)	48e (176)
25	**L10b** (*S*,*S*)	*i*-Pr	rt, 240 h, CH_2Cl_2	nd[e] (26)	nd[e] (*S*)	0 (80)	48e (176)
26	**L12b** (*S*)	*i*-Pr	rt, 48 h, CH_2Cl_2	24 (93)	*R* (*S*)	8 (98)	48e

[a] Reaction conditions are only given for thiazoline ligands. [b] For comparison, the data for the corresponding oxazolines are given in parentheses. [c] In parentheses is given the reference for the corresponding oxazoline if different from that of thiazoline. [d] Corrected assignments of the configurations are given; see ref 48e. [e] nd: not determined.

Table 11. Thiazoline Ligands in Diels−Alder Reaction between Cyclopentadiene and 2-Acryloyloxazolidinone[167]

entry	ligand L[a]	*T* (°C), time	yield (%) thia (oxa)[b]	Ratio endo:exo thia (oxa)[b]	ee (%) thia (oxa)[b]	product config thia (oxa)[b]
1	**L13**	0, 3 h	97	87:13	2	*R*
2	**L14**	0, 24 h	88	91:9	16	*S*
3	**L15**	0, 1 h	92 (95)	87:13 (76:24)	76 (57)	*R* (*R*)
4	**L15**	−60, 36 h	81 (94)	97:3 (84:16)	92 (73)	*R* (*R*)

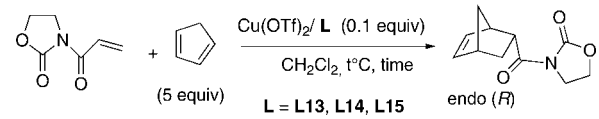
[a] In the synthesis of ligands **L13** and **L14** the starting enantiopure 2-aminoalcohol had the (1*S*,2*R*) configuration. [b] For comparison, data for the corresponding oxazolines are given in parentheses.

5.2. Allylic Substitution

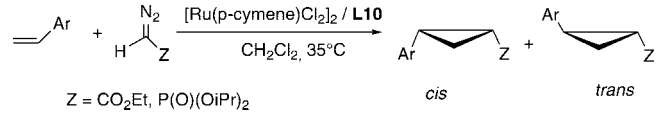
The palladium-catalyzed allylic substitution reaction is a powerful methodology for carbon−carbon bond formation. Design of chiral ligands, among them the famous phosphine−oxazolines developed by Helmchen, Pfaltz, and Williams, has enabled obtaining high enantioselectivities in the asymmetric version of the reaction. The reaction was carried out in toluene using 2.5 mol % of both $[Pd(C_3H_5)Cl]_2$ and ligand **L2a** (R = Et), 2 equiv of BSA, and 10 mol % of AcOK. A systematic study allowed defining the best conditions (CH_2Cl_2, rt) and comparing the results with those obtained with the oxazoline counterparts.

Thiazolines **L2a−c** afforded better catalytic activity than the corresponding oxazolines, which gave 10−20% conversion after 7 days (entries 1−3, Table 10). Dealing with enantioselectivity, thiazolines **L2** proved to be superior to oxazolines.[175] The only exception is with the benzyl thiazoline **L2e**, for which a lower enantioselectivity was measured for a similar conversion (entry 4, Table 10). It is noteworthy that with bis(oxazolines) the enantiomeric excess increased with the bulkiness of substituents, while the opposite effect was observed with thiazolines (best ee = 88% for **L2a** (R = Et)). In most cases, the (*R*,*R*) ligand afforded the (*R*)-enantiomer of *E*-2-methoxycarbonyl-3,5-diphenyl-pent-4-enoate as the major isomer while the (*S*,*S*) derivatives

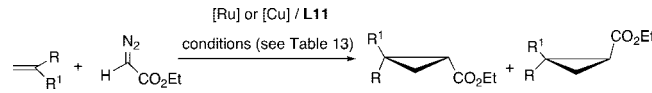
Scheme 79



Scheme 80



Scheme 81



afforded mainly the (*S*)-enantiomer. A noticeable exception was observed with (*S*,*S*) thiazoline **L2c** (R = *t*-Bu), which led to the (*R*) enantiomer as the major isomer (entry 3, Table 10). A competition between nitrogen and sulfur in the chelation to palladium was proposed to explain this unprecedented result.[48e,49] A quantum chemical study on the Pd complexes derived from bis(thiazolines) **L2a** and **L2c** was performed, and the obtained theoretical results support the competition between the (*N*,*N*) and the (*N*,*S*) palladium

Table 12. Asymmetric Cyclopropanation of Styrene and Its Derivatives with Ethyl Diazoacetate and Isopropyl Diazomethylphopshonate Catalyzed by [Ru]/Thiazoline L10 Catalysts

entry	L (config)	R	substrate Ar	Z	yield (%)[a]	ratio trans/cis	ee trans (%) (config) thia [oxa][b]	ee cis (%)[b] (config) thia [oxa][b]	ref thia (oxa)[c]
1	**L10a** (*R*,*R*)	Et	Ph	CO_2Et	87	13.6:1	84 (1*S*,2*S*) [82 (1*S*,2*S*)]	59 (1*S*,2*R*) [54 (1*S*,2*R*)]	166 (177)
2	**L10b** (*S*,*S*)	*i*-Pr	Ph		89	12.4:1	85 (1*R*,2*R*) [89 (1*R*,2*R*]	65 (1*R*,2*S*) [78 (1*R*,2*S*)]	166 (177)
3	**L10d** (*R*,*R*)	Ph	Ph		86	8.8:1	47 (1*S*,2*S*) [69 (1*S*,2*S*)]	20 (1*S*,2*R*) [41 (1*S*,2*R*)]	166 (177)
4	**L10e** (*S*,*S*)	Bn	Ph		92	10.1:1	60 (1*R*,2*R*) [68 (1*R*,2*R*)]	15 (1*R*,2*S*) [24 (1*R*,2*S*)]	166 (177)
5	**L10a** (*R*,*R*)	Et	*p*-$CF_3C_6H_4$		83	19:1	83 (1*S*,2*S*)	55 (1*S*,2*R*)	166
6	**L10b** (*S*,*S*)	*i*-Pr	*p*-$CF_3C_6H_4$		86	12.5:1	77 (1*R*,2*R*)	48 (1*R*,2*S*)	166
7	**L10d** (*R*,*R*)	Ph	*p*-$CF_3C_6H_4$		89	16.2:1	76 (1*S*,2*S*)	15 (1*S*,2*R*)	166
8	**L10e** (*S*,*S*)	Bn	*p*-$CF_3C_6H_4$		75	12.1:1	45 (1*R*,2*R*)	4 (1*R*,2*S*)	166
9	**L10a** (*R*,*R*)	Et	*p*-MeC_6H_4		84	10.5:1	81 (1*S*,2*S*)	46 (1*S*,2*R*)	166
10	**L10b** (*S*,*S*)	*i*-Pr	*p*-MeC_6H_4		72	9.6	81 (1*R*,2*R*)	54 (1*R*,2*S*)	166
11	**L10d** (*R*,*R*)	Ph	*p*-MeC_6H_4		78	8.6	45 (1*S*,2*S*)	20 (1*S*,2*R*)	166
12	**L10e** (*S*,*S*)	Bn	*p*-MeC_6H_4		97	11.5	58 (1*R*,2*R*)	2 (1*R*,2*S*)	166
13	**L10a** (*R*,*R*)	Et	*p*-$MeOC_6H_4$		96	10.5	85 (1*S*,2*S*)	48 (1*S*,2*R*)	166
14	**L10b** (*S*,*S*)	*i*-Pr	*p*-$MeOC_6H_4$		86	11.6	83 (1*R*,2*R*)	64 (1*R*,2*S*)	166
15	**L10d** (*R*,*R*)	Ph	*p*-$MeOC_6H_4$		81	7.7	53 (1*S*,2*S*)	14 (1*S*,2*R*)	166
16	**L10e** (*S*,*S*)	Bn	*p*-$MeOC_6H_4$		80	7.3	52 (1*R*,2*R*)	4 (1*R*,2*S*)	166
17	**L10a** (*R*,*R*)	Et	Ph	P(O)(O-*i*-Pr)$_2$	62		84[d]	nd[e]	166
18	**L10b** (*S*,*S*)	*i*-Pr	Ph		35		64[d]	nd[e]	166
19	**L10d** (*R*,*R*)	Ph	Ph		18		17[d]	nd[e]	166
20	**L10e** (*S*,*S*)	Bn	Ph		17		17[d]	nd[e]	166

[a] Yields are given for the mixture of *cis*- and *trans*-cyclopropylester. [b] For comparison, the data for the corresponding oxazolines Pybox are given in brackets. [c] In brackets is given the reference for the corresponding oxazoline if different from that of thiazoline. [d] The configuration has not been determined. [e] *cis*-Cyclopropyl esters were formed in too small quantities to be analyzed.

Table 13. Asymmetric Cyclopropanation of Styrene and Its Derivatives with Ethyl Diazoacetate Catalyzed by [Ru] or [Cu] /Thiazoline L11 Catalysts[172]

entry	substrate R, R[1]	catalyst[a]	solvent, *T* (°C)	yield (%)[b]	trans /cis	ee trans (%)[c]	ee cis (%)[c]
1	Ph, H	[$RuCl_2$(*p*-cymene)]$_2$	CH_2Cl_2, 0	44	55:45	0	0
2	Ph, H	Cu(OTf) 0.5Ph H	CH_2Cl_2, 0	65	58:42	28	18
3	Ph, H	Cu(OTf) 0.5Ph H	CH_2Cl_2, −20	no reaction			
4	Ph, H	Cu(OTf) 0.5Ph H	CH_2Cl_2, 35	70	63:37	22	20
5	Ph, H	Cu(OTf) 0.5Ph H	toluene, 0	64	54:46	22	24
6	Ph, H	Cu(OTf) 0.5Ph H	Et_2O, 0	44	61:39	18	16
7	*p*-$MeOC_6H_4$, H	Cu(OTf) 0.5Ph H	CH_2Cl_2, 0	19	70:30	24	10
8	Ph, Ph	[$RuCl_2$(*p*-cymene)]$_2$	CH_2Cl_2, 0	5		0	0
9	Ph, Ph	Cu(OTf) 0.5Ph H	CH_2Cl_2, 0	6		0	0

[a] Ligand **11** (1.1 mol %), metal salt (1 mol %). [b] Isolated yields after chromatography. [c] Determined after separation of isomers.

Table 14. Asymmetric Henry Reactions of α-Ketoesters with Nitromethane Catalyzed by Lewis Acid/Thiazoline L6 Complex

entry	ligand L (config)	R	R[1]	Lewis acid	yield (%)[a] thia (oxa)[b]	ee (%) thia (oxa)[b]	product config thia (oxa)[b]	ref
1	**L6b** (*S*,*S*)	*i*-Pr	CH_3	Cu(OTf)$_2$[c]	76 (90)	47 (50)	*S* (*S*)[d]	43
2	**L6f** (*S*,*S*)	*i*-Bu	CH_3	Cu(OTf)$_2$[c]	40 (56)	8 (49)	*S* (*S*)	43
3	**L6d** (S,S)	Ph	CH_3	Cu(OTf)$_2$[c]	30 (54)	63 (39)	*S* (*S*)	43
4	**L6e** (*S*,*S*)	Bn	CH_3	Cu(OTf)$_2$[c]	75 (61)	9 (56)	*S* (*S*)	43
5	**L6c** (*S*,*S*)	*t*-Bu	CH_3	Cu(OTf)$_2$[c]	55 (74)	70 (60)	*S* (*S*)	43
6	**L6b** (*S*,*S*)	*i*-Pr	CF_3	Cu(OTf)$_2$[c]	88 (52)	10 (11)	*S* (*S*)	43
7	**L6f** (*R*,*R*)	*i*-Bu	CF_3	Cu(OTf)$_2$[c]	12 (23)	0 (6)	(*S*)	43
8	**L6d** (*S*,*S*)	Ph	CF_3	Cu(OTf)$_2$[c]	38 (84)	13 (23)	*S* (*S*)	43
9	**L6c** (*S*,*S*)	*t*-Bu	CF_3	Cu(OTf)$_2$[c]	14 (66)	0 (0)		43
10	**L6b** (*S*,*S*)	*i*-Pr	CH_3	Et_2Zn[d]	56 (80)	38 (77)	*R* (*R*)	169
11	**L6f** (*S*,*S*)	*i*-Bu	CH_3	Et_2Zn[d]	38 (49)	56 (73)	*R* (*R*)	169
12	**L6d** (*S*,*S*)	Ph	CH_3	Et_2Zn[d]	25 (73)	6 (47)	*R* (*R*)	169
13	**L6e** (*S*,*S*)	Bn	CH_3	Et_2Zn[d]	44 (76)	68 (79)	*R* (*R*)	169
14	**L6c** (*S*,*S*)	*t*-Bu	CH_3	Et_2Zn[d]	68 (62)	2 (57)	*R* (*R*)	169

[a] Isolated yields after column chromatography. [b] For comparison, the data for the corresponding oxazoline are given in parentheses. [c] Reactions were performed with 1 equiv of α-ketoester and 64 equiv of CH_3NO_2 in the presence of 20 mol % of Et_3N and 20 mol % of L/Cu(OTf)$_2$ complex. [d] Reactions were performed with 0.25 mmol of ethylpuruvate and 10 mmol of nitromethane in 2 mL of THF, 20 mol % of ligand, and 50 mol % of Et_2Zn.

chelation.[49] With the C_2-symmetric ligands **L3** a high catalytic activity was always observed (entries 5 and 6, Table 10) for a moderate enantioselectivity (41−51%). Unfortunately, no comparative data with bis(oxazolines) are available. With the C_2-symmetric dibenzocycloheptadiene ligands **L4** the best results were obtained at low temperature (0 °C); a high catalytic activity (84−89%) similar to that obtained with the oxazoline counterparts at rt was measured (entries 7−10, Table 10). Significant differences were observed in enantioselectivity. If oxazolines analogues afforded reasonable enantioselectivity (up to 86%), bis(thiazoline) **L4** afforded only low to moderate selectivity (14−56%). It is noteworthy that an inversion of configuration in the product was always observed when oxazoline and thiazolines were used (entries 7, 9, 10, Table 10) except when R = Bn (entry 8, Table 10).

Table 15. Asymmetric Catalytic Addition of Nitroethane to β-Nitrostyrene[168]

entry	ligand L (config)	R	R^1	T (°C)	yield (%) thia (oxa)[a]	ratio syn:anti thia (oxa)[a]	ee (%) syn thia (oxa)[a]	product config [b]
1	**L6d** (*R*,*R*)	Ph	Ph	rt	54 (82)	11.7:1 (6.1:1)	95 (91)	2*R*,3*R*
2	**L6c** (*R*,*R*)	*t*-Bu	Ph	rt	nd (21)	nd (only syn)	nd (78)	2*R*,3*R*
3	**L6d** (*R*,*R*)	Ph	4-Me-C_6H_4	30	75 (83)	6.9:1 (6.1:1)	89 (91)	2*R*,3*R*
4	**L6d** (*R*,*R*)	Ph	4-F-C_6H_4	30	79 (80)	9.3:1 (3.9:1)	92 (91)	2*R*,3*R*
5	**L6d** (*R*,*R*)	Ph	2-naphthyl	30	66 (83)	7.4:1 (3.8:1)	88 (88)	2*R*,3*R*

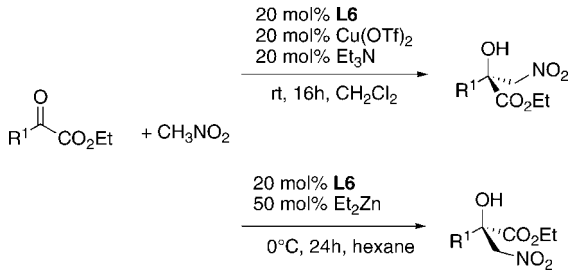
[a] For comparison, the data for the corresponding oxazoline are given in brackets. [b] The same configuration was obtained with thiazoline and oxazoline.

Table 16. Asymmetric Friedel−Crafts Reactions of Indole and Methoxyfuran with Nitroalkenes Catalyzed by ($Zn(OTf)_2$)/Thiazoline L6 Complex

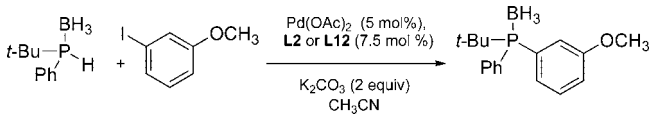
entry	ligand L (config)	R	substrate	yield (%)[a] thia (oxa)[b]	ee (%) thia (oxa)[b]	product config thia (oxa)[b]	ref
1	**L6b** (*S*,*S*)	*i*-Pr	indole	93 (94)	11 (30)	*R* (*R*)	181
2	**L6c** (*S*,*S*)	*t*-Bu	indole	87 (95)	2 (68)	*R* (*R*)	181
3	**L6d** (*S*,*S*)	Ph	indole	99 (99)	78 (83)	*R* (*R*)	181
4	**L6e** (*S*,*S*)	Bn	indole	99 (99)	59 (66)	*R* (*R*)	181
5	**L6f** (*S*,*S*)	*i*-Bu	indole	95 (85)	46 (71)	*R* (*R*)	181
6	**L6b** (*S*,*S*)	*i*-Pr	methoxyfuran	15 (31)	67 (78)	*S* (*S*)	182
7	**L6c** (*S*,*S*)	*t*-Bu	methoxyfuran	6 (73)	3 (92)	*S* (*S*)	182
8	**L6d** (*S*,*S*)	Ph	methoxyfuran	66 (65)	84 (87)	*S* (*S*)	182
9	**L6e** (*S*,*S*)	Bn	methoxyfuran	78 (64)	93 (92)	*S* (*S*)	182

[a] Isolated yields after column chromatography. [b] For comparison, the data for the corresponding bis(oxazoline) are given in parentheses.

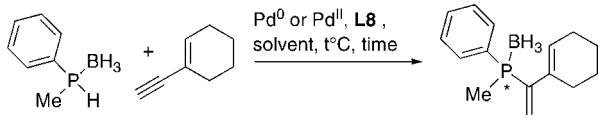
Scheme 82



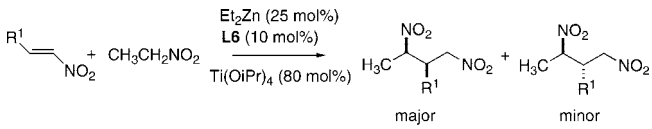
Scheme 83



Scheme 84

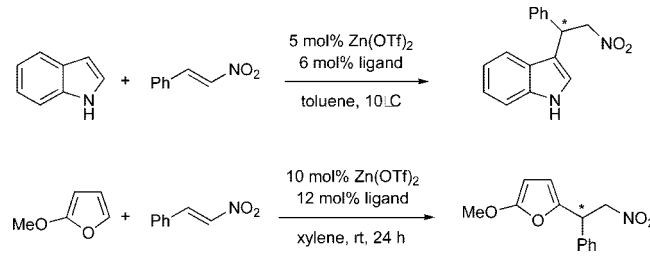


Scheme 85



With pyridylthiazoline **L7** the catalytic activity was always lower than that observed with the corresponding oxazolines[176] (entries 11−15, Table 10). About 2 h are required with pyridyl oxazolines to obtain high conversion, while 3−4 days are needed with thiazoline derivatives **L7**. Enantiomeric excesses are quite similar with a small superiority for thiazolines derivatives (best ee = 81% ee with R = *t*-Bu, entry 14, Table 10). The same enantiomer was obtained with both ligands; the (*R*)-isomer of the product was obtained when using the (*R*)-ligand and (*S*)-isomer when using the (*S*)-ligand, which suggests that the reaction intermediates are the same whatever the ligand used.

Scheme 86



2-Quinolyl thiazolines **L8** gave quite similar results to pyridylthiazolines **L7**. Their catalytic activity was always lower than that of their analogous oxygen derivatives.[176] About 72−144 h are required for reasonable conversion using thiazolines compared to 4−17 h for the corresponding oxazolines. Dealing with enantioselectivity, the results are very close and the enantioselectivity increases when the steric hindrance increases. The best ee results were obtained with the *t*-Bu derivatives (85% for thiazoline **L8c** and 92% ee for the analogous oxazoline, entry 19, Table 10). These values are close to those obtained with the pyridyl thiazoline **L7c** (81% ee, entry 14, Table 10), suggesting a similar intermediate in the mechanism.

The 8-quinolyl thiazolines **L9**, which could lead with palladium to formation of a 6-membered chelate ring, were also tested and compared to their oxygen counterparts and **L8**. The 8-quinolyl thiazolines **L9** proved to be rather inefficient to promote the reaction (8−20% conversion after 10 days, entries 21−24, Table 10) in contrast to their corresponding oxazoline analogues and ligands **L8**. Furthermore, low enantiomeric excesses were obtained (13−48%).

Pyridyl bis(thiazoline) **L10b** (R = *i*-Pr) proved to be inefficient to promote allylic alkylation whatever the conditions used (entry 25, Table 10). This result was not unexpected since the reaction was reported to be rather slow with the corresponding oxygen analogue, e.g., the famous Pybox ligand; 2 days were required to obtain a reasonable conversion (88%). The phosphine thiazoline ligand **L12** also gave disappointing results (8% conversion and 24% ee, entry

26, Table 10) if compared with its famous oxazoline analogue the PHOX ligand (93% ee and 98% conversion in 2 days at rt).

5.3. Diels−Alder Reaction

Sterically congested "roofed" 2-thiazolines **L13**, **L14**, and **L15** were tested in the copper-catalyzed enantioselective Diels−Alder reaction between 3-acryloyl-oxazolidinone and cyclopentadiene (Scheme 79).[167] The best precatalyst defined in a test reaction using 0.1 equiv of thiazoline **L13−15** and an equimolar amount of copper precatalyst [$Cu(OTf)_2$, $CuCl_2$, $Cu(acac)_2$, $Cu(ClO_4)_2$, or $Cu(SbF_6)_2$] showed the superiority of the SbF_6 counteranion for the reaction rate and the OTf anion for the enantioselectivity. The test of ligands **L13−15** was then performed using the OTf anion (Table 11). Bis(thiazoline) ligand **L13** (entry 1, Table 11) and pyridyl−thiazoline **L14** (entry 2, Table 11) afforded high yields, a good *endo:exo* ratio (>87:13), but poor enantioselectivity (<16%). In contrast, (2-diphenylphosphino)phenylthiazoline **L15** (entry 3, Table 11) afforded a high yield, a good *endo:exo* ratio (87:13), and reasonable enantioselectivity (76%). A decrease in temperature (−60 °C) proved to be beneficial for both the *endo/exo* ratio (97:3) and the ee (92%). It is worth noting that the analogous phosphine−oxazoline gave lower dia- and enantioselectivities whatever the conditions used (entries 3 and 4, Table 11).

Nishio et al. reported the use of zinc triflate to catalyze the reaction. With **L5**-type bis(thiazoline), the expected cycloadducts were obtained with good diastereoselectivity (96:4) and excellent enantioselectivity for the major diastereoisomer (ee = 92%).[170]

5.4. Cyclopropanation

The asymmetric cyclopropanation of alkenes with diazoesters catalyzed by transition metals has been intensively studied. Ruthenium catalysts having bis(oxazolinyl)pyridine ligands (Pybox) are among the most efficient. Analogous homochiral 2,6-bis(thiazolinyl)pyridines **L10** were recently tested in the asymmetric ruthenium-catalyzed cyclopropanation of styrene derivatives with ethyl diazoacetate, which is used as a benchmark reaction for new ligand structures and in a more original reaction using methyldiazophosphonate (Scheme 80).[166] The reaction was performed in dichloromethane at 35 °C using a 1:200:1000 ratio of catalyst:diazoester:substrate.

With ethyldiazoacetate the cyclopropanation occurs with a high yield whatever the styrene derivative and ligand used (entries 1−16, Table 12). The yields with diazophosphonates were comparatively rather low (entries 17−20, Table 12). With styrene ligands **L10** having an ethyl or isopropyl group (entries 1 and 2, Table 12) proved to be superior in terms of diastereoselectivity (*trans* isomer as the major product) than the phenyl and benzyl ones (entries 3 and 4, Table 12). Dealing with enantioselectivity, the *trans*-isomer was always obtained with a better enantioselectivity than the *cis* derivative (entries 1−4, Table 12). A high level of enantioselectivity (>80%), comparable to those reported with ruthenium bis(oxazoline) complexes,[177] was obtained with ligands **L10a,b** (R = Et, *i*-Pr) (entries 1 and 2, Table 12). By contrast, phenyl or benzyl derivatives **L10d,e** afforded a lower level of enantioselection (<60%). The same configuration was obtained for the main enantiomer for both oxazolines and thiazolines, indicating no specific effect of the replacement of the oxygen atom by a sulfur atom in this reaction. Variation on the substrate did not change the level of enantioselection nor the sense of induction (entries 5−16, Table 12), indicating a weak electronic effect of the substrate on the enantioselectivity.

The ruthenium−thiazoline catalysts also catalyzed styrene cyclopropanation with diisopropyldiazomethyl phosphonate. Although the reaction required a longer time with phosphonate than with diazoacetate (12 h compared to 1 h) with ligand **L10a**, the ee values were quite similar (84%) (entries 1 and 17, Table 12). With the other ligands **L10b**, **L10d**, and **L10e** yields and enantioselectivities were rather poor (entries 18−20, Table 12).

In 2007 Boysen et al. reported the synthesis of a carbohydrate-derived pyridyl bis(thiazoline) **L11**.[172] This compound was used in the ruthenium-catalyzed cyclopropanation of styrene derivatives with ethyl diazoacetate using the same protocol as reported for ligand **L10** (Scheme 81). The expected cyclopropane derivative was obtained in racemic form in poor yield (44%). However, when the reaction was performed in dichloromethane at 0 °C using copper(I) triflate, a high yield together with a low diastereoselectivity and enantioselectivity were obtained (entry 2, Table 13). Lowering the temperature or modifying the solvent did not improve the selectivity (entries 3−6, Table 13). Two other alkenes, 4-methoxystyrene and 1,1-diphenylethylene, were also used. The expected products were obtained, however, in low yield and poor selectivities.

5.5. Henry Reaction

The Henry or nitroaldol reaction is a powerful methodology for C−C bond formation. Moreover, the resulting beta-nitroalkanol can undergo a large range of chemical transformations. Bis(oxazoline) ligands are one of the most efficient ligands in the asymmetric version of the reaction; C_2-symmetric tridentate bis(thiazoline) derivatives were recently tested in this reaction and compared with their oxygen counterparts.[43,169] The reaction between ethylpyruvate or its fluorinated derivative and nitromethane was selected as a model reaction (Scheme 82). When the reactions were performed at rt with 20 mol % of $Cu(OTf)_2$/thiazoline complex and 20 mol % of Et_3N, bis(thiazolines) proved to be efficient to catalyze the reaction; however, most of the time they afforded a lower catalytic activity compared to their oxazoline counterparts (Table 14). The only noticeable exception is with ligand **L6b** and substrate having a trifluoromethyl group, for which a high yield of 88% was obtained (entry 6, Table 14). The enantioselectivities were rather low except when **L6c** (R = *t*-Bu) is used (ee = 70%) (entry 5, Table 14). With (*S*,*S*) ligands the (*S*) absolute configuration of the Henry product was observed with both the bis(oxazoline) and the bis(thiazoline) ligands. Interestingly, a reversal of enantioselectivity in the reaction was achieved with the same chiral ligand by changing the Lewis acid center from copper(II) to zinc(II). With this Lewis acid and bis(thiazolines) **L6** yields between 25% and 68% and enantioselectivities up to 68% (**L6e**, R = Bn) were obtained (entries 10−14, Table 14). Whatever the substitution pattern on bis(thiazolines), bis(oxazolines) proved to be superior for enantioselectivity (ee = 47−79%). Enantioselectivities were further improved by moving from THF to hexane and lowering the temperature to 0 °C with ligand **L6e**.

5.6. C−P Bond Formation

Chiral phosphines are valuable ligands for asymmetric catalysis. Since a few years ago, new methodologies allowing the preparation of chiral phosphines by asymmetric catalysis have emerged.[178] Thiazolines have been tested as chiral ligands in two of these reactions: palladium-catalyzed C−P cross-coupling[179] and palladium-catalyzed hydrophosphination of alkynes.[180]

The palladium-catalyzed C−P cross coupling reaction was performed between *tert*-butylphenylphosphine−borane and *m*-iodoanisole in the presence of $Pd(OAc)_2$ (5 mol %), thiazoline ligand **L2** or **L12** (7.5 mol %), and K_2CO_3 (2 equiv) in acetonitrile at 40 °C (Scheme 83). Bis(thiazoline) **L2a** (R = Et) afforded a reasonable conversion for a promising enantioselectivity (13%) in a preliminary test. Under the same conditions, racemic tertiary phosphine−borane was obtained with the analogous bis(oxazoline). Phosphine−thiazoline **L12** was unable to catalyze the reaction, while its oxygen counterpart, the well-known phosphine−oxazoline developed by Pfaltz and Helmchen, gave the best ee obtained in this reaction (27% ee at 40 °C and 45% at rt).

The hydrophosphination reaction of alkynes was performed using methylphenylphosphine−borane and cyclohexenylethyne in toluene using 5 mol % of $Pd(OAc)_2$ and 7.5 mol % of ligand (Scheme 84). Various ligands were tested, among them thiazoline **L8** (R = *i*-Pr). Unfortunately, **L8** prove to be inefficient to promote the hydrophosphination reaction, the best ligand from an enantioselective point of view being an electron-rich bis(phosphine), Me-Duphos.

5.7. Addition of Nitroalkanes to Nitroalkenes

The conjugate addition of nitroalkanes to nitroalkenes is an interesting reaction because the reaction products, that is the 1,3-dinitro compounds, open the way to the synthesis of a variety of 1,3-difunctionalized compounds such as heterocycles, carbohydrate derivatives, active energetic materials, etc. Du was the first to propose a zinc-catalyzed access to such dinitro compounds.[168] Ligands **L6** and their oxazoline counterparts were tested in the Michael addition of β-nitroalkanes to nitroalkenes. The reaction was performed using 25 mol % Et_2Zn, 10 mol % of ligand, and 80 mol % of $Ti(O\text{-}i\text{-}Pr)_4$, which was used to activate the zinc catalyst via an "ate" complex (Scheme 85, Table 15). An excess of nitroethane (4 equiv) and apolar solvents (a mixture of toluene and hexane) were required to obtain a good activity and selectivity. The major Michael adduct obtained was the syn adduct whatever the ligand used. Although similar enantiofacial selectivity was obtained with both thiazoline and oxazoline ligands, a higher diastereoselectivity was always observed with thiazolines. With nitrostyrene (R^1 = Ph) the highest enantioselectivity was obtained with ligand **L6d** (ee = 95% for a 54% yield; entry 1, Table 10). The corresponding oxazoline afforded a slightly lower ee (91%) but gave a higher yield (82%).

5.8. Friedel−Crafts Alkylation

The Friedel−Crafts reaction is a powerful methodology for construction of C−C bonds. Interest in using nitroalkenes as substrates in the catalytic asymmetric version of the reaction has recently been demonstrated.[168] In 2006 Du reported the use of thiazolines **L6** and the analogous oxazolines in the zinc-catalyzed asymmetric Friedel−Crafts alkylation of indoles[181] and 2-methoxyfuran[182] with nitroalkenes (Scheme 86).

The reaction with indole was performed using 5 mol % of $Zn(OTf)_2$ as the Lewis acid in toluene. Although good yields in the expected products (85−99%) were observed with both ligands, better enantioselectivities were always obtained with bis(oxazolines) (entries 1−5, Table16). The best value arose from the phenyl-substituted derivatives (78% for thiazoline **L6d** and 83% for the corresponding oxazoline, entry 3, Table 16). With methoxyfuran the results strongly depend on the substitution pattern on the oxazoline and thiazoline (entries 6−9, Table 16). With the *i*-Pr substituent a modest yield and reasonable enantioselectivity were obtained with both thiazoline **L6b** (15% yield, 67% ee) and the corresponding oxazoline (31% yield, 78% ee) (entry 6, Table 16). With phenyl and benzyl substituents rather similar yields and enantioselectivities were measured for thiazolines and oxazolines (entries 8 and 9, Table 16). However, with the *t*-Bu substituent a rather surprising result was noticed. Although good selectivity and activity were obtained with oxazoline (92% ee, 73% yield), poor conversion (6%) together with very low selectivity (3% ee) were obtained with thiazoline **L6c** (entry 7, Table 16). This result deserves explanation; however, no information was given by the authors.

Nevertheless, this result parallels the one obtained in our group in the allylic substitution reaction with the *tert*-butylthiazoline **L2c**[48e,49] and raised again the question of a competition between nitrogen and sulfur in the chelation to the metal.

Different classes of ferrocenyl thiazolines such as **L16**−**L20** have also been recently designed for ligand purposes.[171] However, to date, no information about their use in catalysis has been reported.

6. Conclusion

Since the pioneering work on thiazolines, numerous applications in various fields such as organic synthesis, medicine, agrochemistry, and catalysis have been found for these new heterocyclic compounds. The past 6 years, in particular, have seen a considerable expansion of this research area with the synthesis and application of a plethora of novel structures. These new thiazolines are now efficiently prepared either from amino thiols or from amino alcohols. In the last case, new synthetic methodologies, which use the convenient thiocarbonyl instead of the nasty P_4S_{10} or Lawesson reagent, provide a fantastic opportunity to create structural diversity and efficiently tune the properties of these compounds. This facet is of particular importance for the tailoring of the biological and catalytic properties. However, structure−relationship properties in the biological field as well as in the catalytic field still have to be established for many of these derivatives in order to fully exploit their original properties. Thiazolines are also valuable sources of aldehydes, amino thiols, thiazoles, and thiazolinium salts. In our opinion, the research presented here has clearly established that thiazolines can offer specific properties that their widely used oxygen analogues, i.e., oxazolines, do not possess, especially in the fields of biology and medicine. In catalysis, thiazolines should be considered as a new exciting family of compounds and not only as sulfur analogues of oxazolines. Of particular interest is the fact that in catalysis they can give rise to C_2- or C_1-symmetric ligands depending on the atoms which chelate the metal [(*N,N*) or (*N,S*) chelation]. It is worth noting

that the chemistry of thiazoline derivatives still remains in its infancy and that its true potential has not yet been fully recognized. It is likely that new developments will occur in the near future, taking full advantage of the specific properties of the sulfur atom.

7. Acknowledgments

We thank all the present and former co-workers of the group (http://lcmt.ensicaen.fr/acg) whose names appear in the relevant publications. Special acknowledgments are due to Dr. Serge Masson, who retired in 2004, for his contribution to sulfur chemistry. The work of the group has been performed within the Institute of Chemistry (INC3M FR 3038) and financially supported by the "Ministère de la Recherche et des Nouvelles Technologies", the CNRS, the "Région Basse-Normandie", and the European Union (FED-ER funding).

8. References

(1) (a) Meyers, A. I. In *Heterocycles in Organic Synthesis*; Taylor, E. C.; Weissberger, A., Eds.; Wiley: New York, 1974. (b) Eicher, T.; Hauptman, S. Speicher, A. In *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*; Wiley-VCH: New York, 2003. (c) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*; Elsevier Science: Amsterdam, 2000.
(2) Reviews: (a) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (b) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. (c) Le Perchec, P. *Jansen Chim. Acta* **1986**, *4*, 17.
(3) (a) Reviews: Lutomski, K. A.; Meyers, A. I. Asymmetric Synthesis *via* Chiral Oxazolines. In *Asymmetric Synthesis*; Academic Press: New York, 1984; Vol. 3, p 213. (b) Pfaltz, A. *J. Heterocycl. Chem.* **1999**, *36*, 1437. (c) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151.
(4) Reviews: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (c) Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 680. (d) Desimoni, G.; Faita, G.; Jorgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.
(5) Fustero, S.; Salavert, E.; Navarro, A.; Mojarrad, F.; Fuentes, A. S. In *Targets in Heterocyclic Systems*; Attanasi, O. A.; Spinelli, D., Eds.; Italian Society of Chemistry: 2001; Vol. 5, pp 235−270.
(6) Kwiatkowski, S.; Crocker, P. J.; Chavan, A. J.; Imai, N.; Haley, B. E.; Watt, D. S.; Ho, R.-j. *Tetrahedron Lett.* **1990**, *31*, 2093.
(7) Boyce, R. J.; Mulkueen, G. C.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 5705.
(8) Ramasamy, K. S.; Bandaru, R.; Averett, D. *J. Org. Chem.* **2000**, *65*, 5849.
(9) Yamakuchi, M.; Matsunaga, H.; Tokuda, R.; Ishizuka, T.; Nakajima, M.; Kunieda, T. *Tetrahedron Lett.* **2005**, *46*, 4019.
(10) Ehrler, J.; Farooq, S. *Synlett* **1994**, 702.
(11) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471.
(12) Wipf, P.; Wang, X. *J. Comb. Chem.* **2002**, *4*, 656.
(13) Busacca, C. A.; Dong, Y.; Spinelli, E. M. *Tetrahedron Lett.* **1996**, *37*, 2935.
(14) Padmavathi, V.; Reddy, B. C. O.; Mohan, A. V. N.; Padmaja, A. *J. Heterocycl. Chem.* **2007**, *44*, 459.
(15) North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267.
(16) Katritzky, A. R.; Cai, C.; Suzuki, K.; Singh, S. K. *J. Org. Chem.* **2004**, *69*, 811.
(17) Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908.
(18) Fukuhara, T.; Hasegawa, C.; Hara, S. *Synthesis* **2007**, *10*, 1528.
(19) Kamila, S.; Biehl, E. R. *J. Heterocycl. Chem.* **2007**, *44*, 407.
(20) Fernandez, X.; Fellous, R.; Duñach, E. *Tetrahedron Lett.* **2000**, *41*, 3381.
(21) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5566.
(22) (a) Parsons, R. L.; Heathcock, C. H. *J. Org. Chem.* **1994**, *59*, 4733. (b) Akaji, K.; Kiso, Y. *Tetrahedron* **1999**, *55*, 10685.
(23) Raman, P.; Razavi, H.; Kelly, J. W. *Org. Lett.* **2000**, *2*, 3289.
(24) Sakakura, A.; Kondo, R.; Umemura, S.; Ishihara, K. *Adv. Synth. Catal.* **2007**, *349*, 1641.
(25) For general syntheses of thioamides, see: (a) Hurd, R. N.; Delamater, G. *Chem. Rev.* **1961**, *61*, 45. (b) Bauer, W.; Kühlein, K. *Houben-Weyl's Methoden der Organischen Chemie*; Georg Thieme Verlag: Stuttgart, New York, 1985; Vol. E5, pp 1218−1279. (c) Schaumann, E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp 419−434. (d) Jagodzinski, T. S. *Chem. Rev.* **2003**, *103*, 197.
(26) (a) Wenker, H. *J. Am. Chem. Soc.* **1935**, *57*, 1079. (b) Bach, G.; Zahn, M. *J. Prakt. Chem.* **1959**, *8*, 68. (c) Roggero, J.; Metzger, J. *Bull. Soc. Chim. Fr.* **1963**, 2533. (d) Handrick, G. R.; Atkinson, E. R.; Granchelli, F. E.; Bruni, R. J. *J. Med. Chem.* **1965**, *8*, 762.
(27) For a recent review on Lawesson's reagent, see: Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210.
(28) (a) Scheibye, S.; Pedersen, B. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229. (b) Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* **1984**, *40*, 2047. (c) Jensen, O. E.; Lawesson, S.-O.; Bardi, R.; Piazzesi, A. M.; Toniolo, C. *Tetrahedron* **1985**, *41*, 5595. (d) Unverzagt, C.; Geyer, A.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1229.
(29) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) Hudlicky, M. *Org. React.* **1988**, *35*, 513.
(30) Lal, G. S.; Pez, G. P.; Pesarezi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048.
(31) (a) Atkins, G. M., Jr.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A.; Williams, W. M. *Org. Synth.* **1977**, *56*, 40.
(32) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
(33) Lafargue, P.; Guenot, P.; Lellouche, J. P. *Synlett* **1995**, *2*, 171.
(34) Mahler, S. M.; Serra, G. L.; Antonow, D.; Manta, E. *Tetrahedron Lett.* **2001**, *42*, 8143.
(35) (a) Wipf, P.; Miller, C. P.; Venkatraman, S.; Fritch, P. C. *Tetrahedron Lett.* **1995**, *36*, 6395. (b) Wipf, P.; Fritch, P. C. *J. Am. Chem. Soc.* **1996**, *118*, 12358. (c) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (d) Wipf, P.; Fritch, P. *Tetrahedron Lett.* **1994**, *35*, 5397.
(36) Ino, A.; Murabayashi, A. *Tetrahedron* **2001**, *57*, 1897.
(37) Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659.
(38) Mitsunobu, O. *Synthesis* **1981**, 1.
(39) (a) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807. (b) Takahata, H.; Ohkura, E.; Ikuro, K.; Yamazaky, T. *Synth. Commun.* **1990**, *20*, 285. (c) Wipf, P.; Miller, C. *Tetrahedron Lett.* **1992**, *33*, 6267.
(40) (a) Ritter, T. K.; Wong, C.-H. *Tetrahedron Lett.* **2001**, *42*, 615. (b) Knapp, S.; Yang, C.; Haimowitz, T. *Tetrahedron Lett.* **2002**, *43*, 7101.
(41) Aitken, R. A.; Armstrong, D. P.; Galt, R. H. B.; Mesher, S. T. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 935.
(42) Fu, B.; Du, D.-M.; Xia, Q. *Synthesis* **2004**, 221.
(43) Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433 Corrigendum in Tetrahedron: Asymmetry 2005, 16, 1409Corrigendum in Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1409.
(44) Guirado, A.; Andreu, R.; Martiz, B.; Pérez-Ballester, S. *Tetrahedron* **2006**, *62*, 9688.
(45) Wipf, P.; Uto, Y. *Tetrahedron Lett.* **1999**, *40*, 5165.
(46) Tomalia, D. A.; Paige, J. N. *J. Org. Chem.* **1973**, *38*, 3949.
(47) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257.
(48) (a) Leflemme, N.; Marchand, P.; Gulea, M.; Masson, S. *Synthesis* **2000**, 1143. (b) Pfund, E.; Lequeux, T.; Masson, S.; Vazeux, M. *Org. Lett.* **2002**, *4*, 843. (c) Abrunhosa, I.; Gulea, M.; Levillain, J.; Masson, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2851. (d) Dominguez, Z. J.; Marchand, P.; Gulea, M.; Masson, S. *Carbohydr. Res.* **2005**, *340/4*, 579. (e) Abrunhosa, I.; Delain-Bioton, L.; Gaumont, A.-C.; Gulea, M.; Masson, S. *Tetrahedron* **2004**, *60*, 9263.
(49) Betz, A.; Yu, L.; Reiher, M.; Gaumont, A.-C.; Gulea, M.; Jaffrès, P.-A. *J. Organomet. Chem.* **2008**, *693*, 2499.
(50) For general syntheses of dithioesters, see: Glass, R. S. *Sci. Synth.* **2005**, *22*, 109–133.
(51) Boden, C. D. J.; Norley, M. C.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 9111.
(52) Muir, J. C.; Pattenden, G.; Ye, T. *Tetrahedron Lett.* **1998**, *39*, 2861.
(53) Liu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595.
(54) Nötzel, M. W.; Labahn, T.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, 3025.
(55) Attanasi, O. A.; De Crescentini, L.; Foresti, E.; Galarini, R.; Santeusanio, S.; Serra-Zanetti, F. *Synthesis* **1995**, 1397.
(56) Attanasi, O. A.; Berretta, S.; De Crescentini, L.; Favi, G.; Filippone, P.; Giorgi, G.; Lillini, S.; Mantellini, F. *Tetrahedron Lett.* **2007**, *48*, 2449.
(57) Castan, F.; Denonne, F.; Bigg, D. C. H. *Synthesis* **1993**, 1081.
(58) Fukuyama, T.; Xu, L. *J. Am. Chem. Soc.* **1993**, *115*, 8449.
(59) Brossmer, R.; Mack, H. *Tetrahedron Lett.* **1981**, *22*, 933.
(60) Chen, J.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 1281.
(61) Garciá Martínez, A.; Teso Vilar, E.; Moreno-Jiménez, F.; Álvarez Garciá, A. M. *Tetrahedron: Asymmetry* **2006**, *17*, 2970.
(62) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Tetrahedron: Asymmetry* **2002**, *13*, 429.
(63) (a) Engman, L. *J. Org. Chem.* **1991**, *56*, 3425. (b) Petragnani, N.; Stefani, H. A.; Valduga, C. J. *Tetrahedron* **2001**, *57*, 1411.

(64) Aitken, R. A.; McGill, S. D. *Phosphorus, Sulfur, Silicon Related Elem.* **2005**, *180*, 1519.
(65) (a) Meyers, A. I. *J. Org. Chem.* **1960**, *25*, 1147. (b) Meyers, A. I.; Durandetta, J. L. *J. Org. Chem.* **1975**, *40*, 2021. (c) Meyers, A. I.; Munavu, R.; Durandetta, J. *Tetrahedron Lett.* **1972**, 3929.
(66) Meyers, A. I.; Durandetta, J. L.; Munavu, R. *J. Org. Chem.* **1975**, *40*, 2025.
(67) Laduranty, J.; Barbot, F.; Miginiac, L. *Bull. Soc. Chim. Fr.* **1989**, *6*, 850.
(68) For a recent review on thiazoles, see: Dondoni, A.; Marra, A. *Chem. Rev.* **2004**, *104*, 2557.
(69) (a) Tavares, F.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 6803. (b) Tavares, F.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 8207.
(70) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331.
(71) Thiazofurin is the generic name approved by the United States Adopted Name Council.
(72) Brown, R. S.; Dowden, J.; Moreau, C.; Potter, B. V. L. *Tetrahedron Lett.* **2002**, *43*, 6561.
(73) Mislin, G. L.; Burger, A.; Abdallah, M. A. *Tetrahedron* **2004**, *60*, 12139.
(74) Martin, R. B.; Lowey, S.; Elson, E. L.; Edsall, J. T. *J. Am. Chem. Soc.* **1959**, *81*, 5089.
(75) Schmir, G. L. *J. Am. Chem. Soc.* **1965**, *87*, 2743.
(76) Kok, G. B.; Campbell, M.; Mackey, B.; von Itzstein, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2811.
(77) Kim, T.-S.; Lee, Y.-J.; Jeong, B.-S.; Park, H.-G.; Jew, S.-S. *J. Org. Chem.* **2006**, *71*, 8276.
(78) (a) Pfaltz, A. *Synlett* **1999**, 835. (b) Jalal, M. A. F.; Hossain, M. B.; van der Helm, D.; Sanders-Loehr, J.; Actis, L. A.; Crosa, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 292. (c) Gerwick, W. H.; Proteau, J.; Nagle, D. G.; Hamel, E.; Blokhin, A.; Slate, D. L. *J. Org. Chem.* **1994**, *59*, 1243. (d) Hayashi, K.; Sato, C.; Hiki, S.; Kumagai, T.; Tamai, S.; Abe, T.; Nagao, Y. *Tetrahedron Lett.* **1999**, *40*, 3761. (e) Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1.
(79) Caujolle, R.; Baziard-Mouysset, G.; Favrot, J. D.; Payard, M.; Loiseau, P. R.; Amarouch, H.; Linas, M. D.; Seguela, J. P.; Loiseau, P. M.; Bories, C.; Gayral, P. *Eur. J. Med. Chem.* **1993**, *28*, 29.
(80) Pfund, E.; Masson, S.; Vazeux, M.; Lequeux, T. *J. Org. Chem.* **2004**, *69*, 4670.
(81) Sakamoto, M.; Miyazawa, K.; Kuwabara, K.; Tomimatsu, Y. *Heterocycles* **1979**, *12*, 231.
(82) Elliot, M. C.; Monk, A. E.; Kruiswijk, E.; Hibbs, D. E.; Jenkins, R. L.; Jones, D. V. *Synlett* **1999**, 1379.
(83) Abrunhosa, I. Ph.D. Dissertation, Université de Caen, 2003.
(84) Fisher, N. I.; Hamer, F. M. *J. Chem. Soc. (C)* **1933**, 189.
(85) Maguet, M.; Poirier, Y.; Guglielmetti, R. *C. R. Acad. Sci. Paris (C)* **1975**, *281*, 567.
(86) (a) Moreda, W.; Forrester, A. R. *Tetrahedron* **1997**, *53*, 12595. (b) Moreda, W.; Forrester, A. R. *Tetrahedron* **1997**, *53*, 12605.
(87) Kawakami, M.; Koya, K.; Ukai, T.; Tatsuta, N.; Ikegawa, A.; Ogawa, K.; Shishido, T.; Chen, L. B. *J. Med. Chem.* **1998**, *41*, 130.
(88) (a) Levillain, J.; Dubant, G.; Abrunhosa, I.; Gulea, M.; Gaumont, A.-C. *Chem. Commun.* **2003**, 2914. (b) Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.-C. *ACS Books Series*; Oxford Press: New York, 2007; Vol. 950, p 246. (c) Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.-C. *Amino Acids* **2008**, *35*, 175.
(89) Maguet, M.; Guglielmetti, R. *Bull. Soc. Chim. Fr.* **1978**, 539.
(90) Clark, A. D.; Sykes, P. *J. Chem. Soc. (C)* **1971**, 103.
(91) Undheim, K.; Eidem, A. *Acta Chem. Scand.* **1970**, *24*, 3129.
(92) Singh, H.; Sarin, R. *Tetrahedron* **1986**, *42*, 1449.
(93) Ferris, A. F.; Salerni, L. O.; Schutz, B. A. *J. Med. Chem.* **1966**, *9*, 391.
(94) Zimmermann, T. *J. Heterocycl. Chem.* **1999**, *36*, 813.
(95) Fischer, H.; Kirchbauer, F.; Früh, A.; Abd-Elzaher, M. M.; Roth, G.; Karl, C. C.; Dede, M. *J. Organomet. Chem.* **2001**, *620*, 165.
(96) Fustero, S.; Diaz, M. D.; Asensio, A.; Navarro, A.; Kong, J.-S.; Aguilar, E. *Tetrahedron* **1999**, *55*, 2695.
(97) Katritzky, A. R.; Donkor, A.; Fang, Y. *J. Org. Chem.* **2001**, *66*, 4041.
(98) (a) Fustero, S.; Diaz, M. D.; Carrió, J. S.; Aguilar, E. *Eur. J. Org. Chem.* **2001**, 1195. (b) Fustero, S.; Navarro, A.; Diaz, D.; de la Torre, M. G.; Asensio, A. *J. Org. Chem.* **1996**, *61*, 8849.
(99) Emtenäs, H.; Alderin, L.; Almqvist, F. *J. Org. Chem.* **2001**, *66*, 6756.
(100) Heimgartner, H. *Phosphorus, Sulfur, Silicon* **1991**, *58*, 281.
(101) Arenal, I.; Bernabé, M.; Cuevas, O.; Alvarez, F. *Tetrahedron* **1983**, *39*, 1387.
(102) Reviews: (a) Roy, R. S.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249. (b) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115. (c) Abreu, P. M.; Branco, P. S. *J. Braz. Chem. Soc.* **2003**, *14*, 675. (d) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771. (e) Lewis, J. R. *Nat. Prod. Rep.* **1998**, 371. (f) Bagley, M. C.; Dale, J. W.; Merritt, E. A.; Xiong, X. *Chem. Rev.* **2005**, *105*, 685.
(103) Reviews:(a) Kumazawa, K. *Food Sci. Technol. Res.* **2006**, *12*, 71. (b) Adams, A.; De Kimpe, N. *Chem. Rev.* **2006**, *106*, 2299. (c) Fernandez, X.; Kerverdo, S.; Duñach, E.; Lizzani-Cuvelier, L. *L'Actualité Chim.* **2002**, 5–14.
(104) (a) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. *Tetrahedron Lett.* **1991**, *32*, 2593.
(105) Jurkiewicz, E.; Jansen, R.; Kunze, B.; Trowitzsch-Kienast, W. *Antiviral Chem. Chemother.* **1992**, *3*, 189.
(106) Jansen, R.; Kunze, B.; Reichenbach, H.; Jurkiewicz, E.; Husmann, G.; Höfle, G. *Liebigs Ann. Chem.* **1992**, 357.
(107) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron* **1995**, *51*, 7321.
(108) Kuriyama, N.; Akaji, K.; Kiso, Y. *Tetrahedron* **1997**, *53*, 8323.
(109) (a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5566. (b) Parsons, R. L.; Heathcock, C. H. *Tetrahedron Lett.* **1994**, *35*, 1379. (c) Akaji, K.; Kuriyama, N.; Kiso, Y. *J. Org. Chem.* **1996**, *61*, 3350.
(110) Boyce, R. J.; Pattenden, G. *Synlett* **1994**, 587.
(111) (a) Pattenden, G.; Thom, S. M. *Synlett* **1992**, 533. (b) Pattenden, G.; Thom, S. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1629.
(112) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1995**, *60*, 7224.
(113) Han, F. S.; Osajima, H.; Cheung, M.; Tokuyama, H.; Fukuyama, T. *Chem. Commun.* **2006**, 1757.
(114) Han, F. S.; Tokuyama, H.; Fukuyama, T. *Chem. Commun.* **2007**, 3444.
(115) Han, F. S.; Osajima, H.; Cheung, M.; Tokuyama, H.; Fukuyama, T. *Chem. Eur. J.* **2007**, *13*, 3026.
(116) Yamaguchi, H.; Nakayama, Y.; Takeda, K.; Tawara, K.; Maeda, K.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1957**, 195.
(117) (a) Fujimoto, H.; Kinoshita, T.; Suzuki, H.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 271. (b) Pestka, S.; Brot, N. *J. Biol. Chem.* **1971**, *246*, 7715. (c) Burns, D. J.; Cundliffe, E. *Eur. J. Biochem.* **1973**, *37*, 570.
(118) Inami, K.; Shiba, T. *Tetrahedron Lett.* **1984**, *25*, 2009.
(119) (a) Inami, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2185. (b) Cram, D. J.; Theander, O.; Jager, H.; Stanfield, M. K. *J. Am. Chem. Soc.* **1963**, *85*, 1430.
(120) Zarantonello, P.; Leslie, C. P.; Ferritto, R.; Kazmierski, W. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 561.
(121) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.
(122) Hawkins, C. J.; Lavin, M. F.; Marshall, K. A.; van den Brenk, A. L.; Watters, D. J. *J. Med. Chem.* **1990**, *33*, 1634.
(123) Zabriskie, T. M.; Foster, M. P.; Stout, T. J.; Clardy, J.; Ireland, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 8080.
(124) McDonald, L. A.; Foster, M. P.; Phillips, D. R.; Ireland, C. M.; Lee, A. Y.; Clardy, J. *J. Org. Chem.* **1992**, *57*, 4616.
(125) Wagner, B.; Schumann, D.; Linne, U.; Koert, U.; Marahiel, M. A. *J. Am. Chem. Soc.* **2006**, *128*, 10513.
(126) Caroll, A. R.; Coll, J. C.; Bourne, D. J.; MacLeod, J. K.; Zabriskie, T. M.; Ireland, C. M.; Bowden, B. F. *Aust. J. Chem.* **1996**, *49*, 659.
(127) Mink, D.; Mecozzi, S.; Rebek, J., Jr. *Tetrahedron Lett.* **1998**, *39*, 5709.
(128) (a) Sone, H.; Kigosbi, H.; Yamada, K. *Tetrahedron* **1997**, *53*, 8149. (b) Ojika, M.; Nemoto, T.; Nakamura, M.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 5057.
(129) (a) Luesch, H.; Yoshida, W. A.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418. (b) Luesch, H.; Yoshida, W. A.; Moore, R. E.; Paul, V. J. *Bioorg. Med. Chem.* **2002**, *10*, 1973.
(130) (a) Konigsberg, W.; Hill, R. J.; Craig, L. C. *J. Org. Chem.* **1961**, *26*, 3867. (b) Yonetani, K.; Hirotsu, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3302.
(131) McKeever, B.; Pattenden, G. *Tetrahedron* **2003**, *59*, 2713.
(132) (a) Higashibayashi, S.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2002**, *43*, 105. (b) Higashibayashi, S. T.; Mori, T.; Shinko, K.; Hashimoto, K.; Nakata, M. *Heterocycles* **2002**, *57*, 111.
(133) (a) Nicolaou, K. C.; Nevalainen, M.; Zak, M.; Bulat, S.; Bella, S.; Safina, B. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3418. (b) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Lee, S. H.; Estrada, A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5087. (c) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Lee, S. H.; Estrada, A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5092. (d) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zécri, F. J.; Bulat, S. *J. Am. Chem. Soc.* **2005**, *127*, 11159. (e) Nicolaou, K. C.; Zak, M.; Safina, B. S.; Estrada, A. A.; Lee, S. H.; Nevalainen, M. *J. Am. Chem. Soc.* **2005**, *127*, 11176.
(134) Higashibayashi, S.; Kohno, M.; Goto, T.; Suzuki, K.; Mori, T.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2004**, *45*, 3707.
(135) Nishimura, H.; Okamoto, S.; Mayama, M.; Ohtsuka, H.; Nakajima, K.; Tawara, K.; Shimohira, M.; Shimaoka, N. J. *Antibiot. Ser. A* **1961**, *14*, 255.

(136) Mori, T.; Higashibayashi, S.; Goto, T.; Kohno, M.; Satouchi, Y.; Shinko, K.; Suzuki, K.; Suzuki, S.; Tohmiya, H.; Hashimoto, K.; Nakata, M. *Tetrahedron Lett.* **2007**, *48*, 1331.
(137) Johnson, B. A.; Anker, H.; Meleney, F. L. *Science* **1945**, *102*, 376.
(138) See references in the following: Lee, J.; Griffin, J. H.; Nicas, T. I. *J. Org. Chem.* **1996**, *61*, 3983.
(139) (a) Cox, C. D.; Rinehart, K. L., Jr.; Moore, M. L.; Cook, J. C., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4256. (b) Ankenbauer, R. G.; Toyokuni, T.; Staley, A.; Rinehart, K. L.; Cox, C. D. *J. Bacteriol.* **1988**, *170*, 5344. (c) Rinehart, K. L.; Staley, A. L.; Wilson, S. R.; Ankenbauer, R. G.; Cox, C. D. *J. Org. Chem.* **1995**, *60*, 2786.
(140) (a) Drechsel, H.; Stephan, H.; Lotz, R.; Haag, H.; Zahner, H.; Hantke, K.; Jung, G. *Liebigs Ann.* **1995**, 1727. (b) Ino, A.; Murabayashi, A. *Tetrahedron* **2001**, *57*, 1897.
(141) Bergeron, R. J.; Wiegand, J.; Dionis, J. B.; Egli-Karmakka, M.; Frei, J.; Huxley-Tencer, A.; Peter, H. H. *J. Med. Chem.* **1991**, *34*, 2072.
(142) Ino, A.; Hasegawa, Y.; Murabayashi, A. *Tetrahedron Lett.* **1998**, *39*, 3509.
(143) Ino, A.; Hasegawa, Y.; Murabayashi, A. *Tetrahedron* **1999**, *55*, 10283.
(144) Kobayashi, S.; Hidaka, S.; Kawamura, Y.; Ozaki, M.; Hayase, Y. *J. Antibiot.* **1998**, *51*, 323.
(145) (a) White, E. H.; McCapra, F.; Field, G. F. *J. Am. Chem. Soc.* **1963**, *85*, 337. (b) Day, J. C.; Tisi, L. C.; Bailey, M. *J. Lumin.* **2004**, *19*, 8.
(146) Niwa, K.; Nakamura, M.; Ohmiya, Y. *FEBS Lett.* **2006**, *580*, 5283.
(147) Jones, L. R.; Goun, E. A.; Shinde, R.; Rothbard, J. B.; Contag, C. H.; Wender, P. A. *J. Am. Chem. Soc.* **2006**, *128*, 6526.
(148) Blokhin, A. V.; Yoo, H. D.; Geralds, R. S.; Nagle, D. G.; Gerwick, W. H.; Hamel, E. *Mol. Pharmacol.* **1995**, *48*, 523.
(149) (a) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1995**, *117*, 5612. (b) White, J. D.; Kim, T.-S.; Nambu, M. *J. Am. Chem. Soc.* **1997**, *119*, 103.
(150) Lai, J.-Y.; Yu, J.; Mekonnen, B.; Falck, J. R. *Tetrahedron Lett.* **1996**, *37*, 7167.
(151) Hoemann, M. Z.; Agrios, K. A.; Aubé, J. *Tetrahedron* **1997**, *53*, 11087.
(152) Wipf, P.; Reeves, J. T.; Balachandran, R.; Day, B. W. *J. Med. Chem.* **2002**, *45*, 1901.
(153) Ong, P. K. C.; Acree, T. E. *J. Agric. Food Chem.* **1998**, *46*, 2282.
(154) Doombos, T.; Peer, H. G. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 711.
(155) Fuganti, C.; Gatti, F. G.; Serra, S. *Tetrahedron* **2007**, *63*, 4762.
(156) Rhlid, R. B.; Fleury, Y.; Blank, I.; Fay, L. B.; Welti, D. H.; Arce Vera, F.; Juillerat, M. A. *J. Agric. Food Chem.* **2002**, *50*, 2350.
(157) Wiesler, D. P.; Schwende, F. J.; Carmack, M.; Novotny, M. *J. Org. Chem.* **1984**, *49*, 882.
(158) Tashiro, T.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2167.
(159) Knapp, S.; Vocadlo, D.; Gao, Z.; Kirk, B.; Lou, J.; Withers, S. G. *J. Am. Chem. Soc.* **1996**, *118*, 6804.
(160) Whitworth, G. E.; Macauley, M. S.; Stubbs, K. A.; Dennis, R. J.; Taylor, E. J.; Davies, G. J.; Greig, I. R.; Vocadlo, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 635.
(161) Knapp, S.; Huhn, R. A.; Amorelli, B. *Org. Synth.* **2007**, *84*, 68.
(162) Knapp, S.; Abdo, M.; Ajayi, K.; Huhn, R. A.; Emge, T. J.; Kim, E. J.; Hanover, J. A. *Org. Lett.* **2007**, *9*, 2321.
(163) Kline, T.; Andersen, N. H.; Harwood, E. A.; Bowman, J.; Malanda, A.; Endsley, S.; Erwin, A. L.; Doyle, M.; Fong, S.; Harris, A. L.; Mendelsohn, B.; Mdluli, K.; Raetz, C. R. H.; Stover, C. K.; Witte, P. R.; Yabannavar, A.; Zhu, S. *J. Med. Chem.* **2002**, *45*, 3112.
(164) Kadam, R. U.; Chavan, A.; Roy, N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 861.
(165) Einsiedel, J.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2533.
(166) Le Maux, P.; Abrunhosa, I.; Berchel, M.; Simonneaux, G.; Gulea, M.; Masson, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2569.
(167) Yamakuchi, M.; Matsunaga, H.; Tokuda, R.; Ishizuka, T.; Nakajima, M.; Kunieda, T. *Tetrahedron Lett.* **2005**, *46*, 4019.
(168) Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, S.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418.
(169) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712.
(170) Nishio, T.; Kodama, Y.; Tsurumi, Y. *Phosphorus, Sulfur, Silicon Relat. Elements* **2005**, *180*, 1449.
(171) (a) Tárraga, A.; Molina, P.; Curiel, D.; Bautista, D. *Tetrahedron: Asymmetry* **2002**, *13*, 1621. (b) Molina, P.; Tárraga, A.; Curiel, D. *Synlett* **2002**, 435. (c) Bernardi, L.; Bonini, B. F.; Comes-Franchini, M.; Femoni, C.; Fochi, M.; Ricci, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1133.
(172) Irmak, M.; Lehnert, T.; Boysen, M. K. M. *Tetrahedron Lett.* **2007**, *48*, 7890.
(173) (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 1297–1330. (b) Mellah, M.; Voiturez, A.; Schultz, E. *Chem. Rev.* **2007**, *107*, 5133.
(174) Brunner, H. In *Organometallics in Synthesis 2*; Werner, H., Ercker, G., Eds.; Springer: Heidelberg, 1989, p 277.
(175) (a) Von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265. (b) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (c) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143. (d) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547.
(176) (a) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1997**, *8*, 3183. Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543. (b) Chelucci, G.; Pinna, G.; Saba, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4027.
(177) Nishiyama, H.; Itoh, Y.; Suwagara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247.
(178) For a review, see: Glueck, D. *Synlett* **2007**, 2627.
(179) Pican, S.; Gaumont, A.-C. *Chem. Commun.* **2005**, 2393.
(180) Join, B.; Mimeau, D.; Delacroix, O.; Gaumont, A.-C. *Chem. Commun.* **2006**, 3249.
(181) Lu, S. F.; Du, D. M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115.
(182) Liu, H.; Xu, J.; Du, D. M. *Org. Lett.* **2007**, *9*, 4725.

CR800189Z