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2-Thiazolines: an update on synthetic methods and catalysis

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2-Thiazolines are important building blocks in organic synthesis and are of great importance in many areas of chemistry. At the end of the last century, the use of 2-thiazolines increased in a significant way, especially in synthesis and catalysis. This review highlights the synthetic and catalytic value of 2-thiazolines in the last two decades. We will discuss the new synthetic methodologies for obtaining these heterocycles including new schemes for accessing their asymmetric versions. Most of the new catalytic applications include a variety of 2-thiazoline ligands containing diverse donor atoms, which in combination with metals like Pd, Ir, and Cu, among others, exhibit remarkable catalytic performances.

1. Introduction

2-Thiazolines are five-membered heterocycles containing a sulfur atom and a nitrogen atom and belong to the 1,3-azole family. Since the first reports of these compounds in the literature, the use of 2-thiazolines has spread to many areas, such as medicinal chemistry,[1] food industry,[2] agrochemicals,[3] materials chemistry,[4] organic syntheses,[5] and catalysis.[6]

In 2009, Gaumont, Gulea and Levillain[7] presented the first review of 2-thiazolines, which summarized the main methods of synthesis, their reactivity to obtain valuable organic compounds and some examples showing their use as ligands in catalysis.

In this update, we will discuss what has happened after 2009 with regard to the chemistry and applications of these heterocyclic compounds. First, we will introduce outstanding

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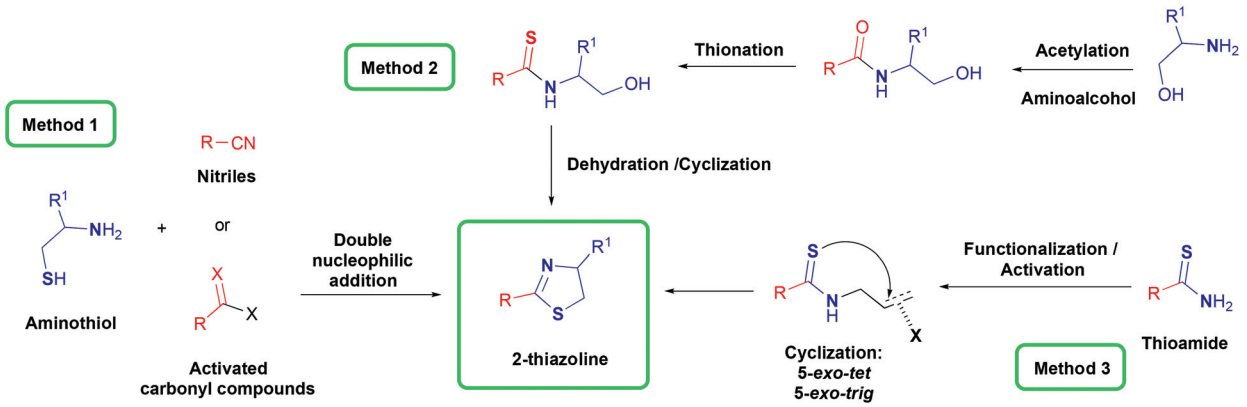

Scheme 1 Summary of the methods for the synthesis of 2-thiazolines.

methods for the synthesis of 2-thiazolines involving catalytic approaches and thioamides that are not derived from amino alcohols as new building blocks of these compounds. This latter route cannot be included in the two classical methods already summarized by Gaumont, Gulea, and Levillain. This new approach involves the functionalization and subsequent activation of commercial thioamides. As advantages, this new method does not need thionating reagents, amino alcohols, or aminothiols, allowing the direct synthesis of and the possibility to access new 4- or 5-substituted thiazolines (Scheme 1).

Then we will outline the use of 2-thiazolines as valuable intermediates to obtain α-alkyl cysteines through catalytic reactions.

In the last part, we will describe a variety of new catalytic applications using diverse ligands containing 2-thiazoline frameworks. The purpose of this review is to show the use of these heterocycles as organic precursors and to give an overview of their advantages in terms of their stability under moisture and high temperature conditions, coordination behavior toward a variety of metal precursors, and performance as ligands in diverse catalytic applications.

2. Recent approaches for the synthesis of 2-thiazolines

In this section, we will discuss new methodologies based on catalytic approaches (metal catalysts or organo-catalysts) and different kinds of starting materials: aminoethanethiols with nitriles, carboxylic acid derivatives, and thioamides that are not derived from amino alcohols.

2.1. From aminoethanethiols and arylnitriles

As we show in Scheme 1, β-amino thiols and β-amino ethanols are the conventional starting materials used to synthesize these compounds. Amino ethanols were considered the most useful precursors until 2009 because they offer better yields,

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although the methods using amino ethanols involve several reaction steps.

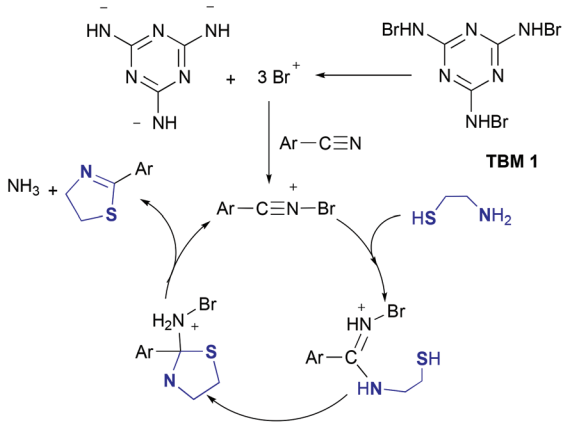
On the other hand, method 1 has not been widely used because the double addition of β-aminoethanethiols to nitriles, carboxylic acids, or activated carbonyl compounds, like esters or imino esters, usually requires difficult reaction conditions, which decreases yields and promotes side reactions or racemization of the final product. Besides, the low availability of commercial β-amino thiols limits the use of this method. However, to overcome this problem, some simple and environmentally friendly catalytic procedures have been reported in the last decade.

Some of these procedures have been successful in making the reaction conditions simpler, and in reducing the use of reagents that are sensitive to humidity or temperature, organocatalysts, solid-supported catalysts, ionic liquids, transition metals, *etc*.

Aryl nitriles are the perfect reagents to synthesize 2-thiazolines through catalytic reactions due to their high commercial availability (Table 1).

For example, 1 mol% of trichloroisocyanuric acid (TCCA)[8] has been tested to achieve the synthesis of these heterocycles, using benzonitrile and 2-aminoethanethiol under solvent-free conditions and 2-phenyl thiazoline was obtained in 95% yield (Table 1, entry 1). Likewise, Dowex-50W-hydrogen ion-exchange resin showed excellent performance in catalyzing the reaction between different aryl nitriles and aminothiol, with products obtained in 88–93% yields under solvent-free conditions (Table 1, entry 2).[9]

On the other hand, in 2012, Liqiang Wu reported on the use of tribromomelanine **1** (TBM) as an efficient organocatalyst for the synthesis of several aryl 2-thiazolines.[10] The best reaction conditions were the use of 0.5 mol% of TBM at 100 °C under solvent-free conditions (Table 1, entry 3). The author proposed that TBM acted as a release agent of Br^+ *in situ*, which promoted the addition of the β-amino thiol after the Br^+ species interacts with the nitrile group, allowing the formation of ammonia as the leaving group (Scheme 2).



Scheme 2 The mechanism of aryl nitrile activation *via* Br^+ species.[10]

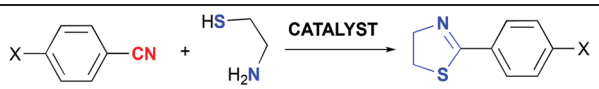
A similar method, where Br^+ was used as the catalyst, was reported using 1-butyl-3-methylimidazolium tribromide ([Bmim]Br_3), a stable ionic liquid.[11] Only 1 mol% of (Bmim)Br_3 was necessary to obtain a 96% yield of the corresponding 2-thiazoline under solvent-free conditions (Table 1, entry 4). Thus, aryl nitriles react efficiently but aliphatic nitriles are not compatible. Likewise, 1,3-dibromo-5,5-dimethylhydantoin (DBH), a bromination agent, works as a homogeneous catalyst in the synthesis of 2-thiazolines as well[12] and 1 mol of DHB was used at 110 °C under solvent-free conditions to obtain 2-phenyl-2-thiazoline in 95% yield and several aryl and pyridyl 2-thiazolines in excellent yields (Table 1, entry 5).

Even though these methods have been developed under solvent-free conditions, the catalysts used in these methods cannot be considered eco-friendly at all. In contrast, cellulose sulfuric acid (CSA), an inexpensive biopolymer-based catalyst, was used in the synthesis of 2-thiazolines.[13] This catalyst was tested in the reaction between 4-chlorobenzonitrile and 2-aminoethanethiol and thiazoline was obtained in 90% yield (Table 1, entry 6).

A similar catalyst containing Fe_3O_4 nanoparticles of agarose was reported by Zarei and Akhlaghinia.[14] The nanoparticle surface was modified using ethanolamine phosphate, where salicylaldehyde was added to obtain a Schiff base and coordinated to a Cu(II) source. Then13 mol% of Fe_3O_4@Agarose/$SAEPH_2$/Cu and 2.5 mol% of NaOH provided the desired thiazoline in 95% yield (Table 1, entry 7). The authors consider that NaOH probably promotes the formation of ammonia as the leaving group, increasing the formation of the product.

On the other hand, in 2013 Garg showed a green method where 1 eq. of Na_2CO_3 in methanol produced 92% yield of 4-bromo-2-phenylthiazoline (Table 1, entry 8).[15] The pathway proposed for this reaction considers that the thiol group carries out the nucleophilic attack on the previously activated nitrile, leading to the formation of **2**, then the thiol group forms the intermediate **3**, which upon the elimination of ammonia affords the thiazoline. Evidence for this plausible

Table 1 Synthesis of 2-thiazolines from aryl nitriles and aminoethanethiols



Entry	Catalyst	Quantity	X	Yield %	Ref.
1	TCCA	1 mol%	H	95	8
2	Dowex-50 W-hydrogen	0.2 g	H	91	9
3	TBM	0.5 mol%	H	98	10
4	[Bmim]Br_3	1 mol%	H	96	11
5	DBH	1 mol%	H	95	12
6	CSA	0.07 g	Cl	90	13
7	Fe_3O_4@Agarose/$SAEPH_2$/Cu	13 mol%	H	95	14
8	Na_2CO_3	1 eq.	Br	92	15
9	NaOH	5 mol%	H	91	17
10	TPA ($H_3PW_{12}O$)	0.5 mol%	H	93	18
11	(SiO_2-TPA) or (C-TPA) or (PMP–TPA)	0.1 mol%	H	95	19
12	$CuCl_2$/2-methacrylic acid	8 mol%	H	87	20

pathway was obtained when disulfide **4** was used and no product was observed. Moreover, the pK_a values for $[HSCH_2CH_2NH_3]^+$ are 8.35 for SH and 10.86 for NH_3^+, indicating that the first deprotonation occurs in the SH group (Scheme 3).[16] Nevertheless, even though the last report represents an improvement in the use of green reagents, the amount of base used is a drawback. In 2015, Cazin *et al.* found that using inorganic bases such as CsOH, KOH, or NaOH in catalytic amounts (5 mol%) promoted the formation of aryl and aliphatic 2-thiazolines with excellent conversions (Table 1, entry 9).[17]

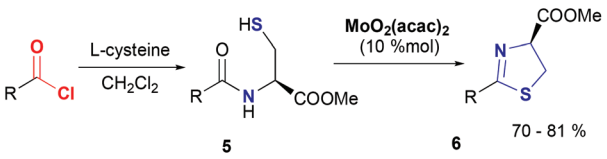
Heteropoly acid catalysts such as TPA ($H_3PW_{12}O$) (Table 1, entry 10),[18] supported in silica gel (SiO_2-TPA), active carbon (C-TPA) and poly-(4-styrylmethyl)pyridinium chloride (PMP–TPA)[19] (Table 1, entry 11), or $CuCl_2$ (Table 1, entry 12)[20] can produce 2-thiazolines in excellent yields. An extensive discussion on these methods can be found in a recent review by Dilruba about synthetic metal-mediated methods to get 2-thiazolines.[21]

2.2. From aminoethanethiols and carboxylic acid, acid halides and other derivatives

Another alternative to synthesize 2-thiazolines is using carboxylic acid derivatives with aminothiols. Before 2009, there are only two reports in the literature on the use of carboxylic acids,[22] two reports on employing esters,[23] and three more on using activated carboxylic acid derivatives.[24]

This route remains the least explored due to the difficult in activation of carboxylic acids or the use of sensitive carboxylic acid derivatives. Despite this, after 2009, some reports were disclosed showing good results. For example, molybdenum precursors were used as agents to promote the cyclodehydration of amide–cysteine derivatives **5**.[25] Only $MoO_2(acac)_2$ (10 mol%) promoted the reaction to obtain thiazolines **6** in good yields (Scheme 4).

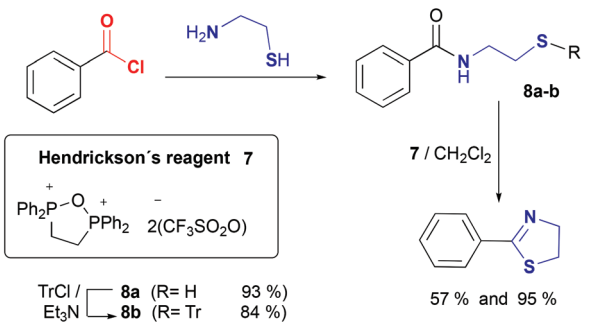
On the other hand, a non-catalytic method was disclosed using the Hendrickson reagent **7**.[26] From benzoyl chloride and 2-aminothiol, the amide **8a** was obtained in 93% yield. Then **8a** reacted with DIPEA and 7 to give 2-phenylthiazoline in 57% yield. To improve this result, the authors decided to protect the thiol group using trityl chloride to obtain the amide **8b**. Then the cyclization of **8b** in the absence of a base gave the thiazoline in 95% yield (Scheme 5).



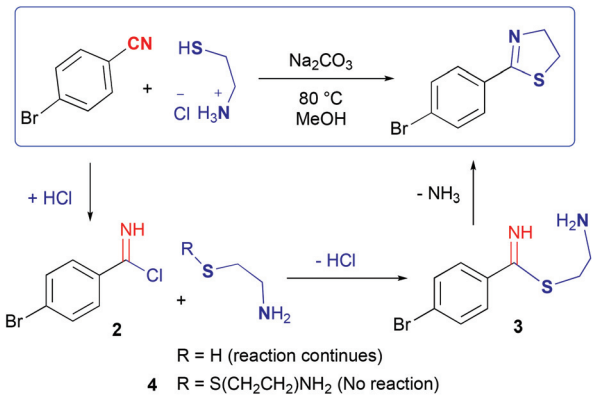
Scheme 4 Synthesis of 2-thiazolines using Mo and carboxylic acid derivatives.[25]

Another strategy starts with β-azido disulfide **9** under one-pot conditions, affording 2-thiazoline in 86% yield.[27] The reaction occurs, thanks to the phosphine triggering a sequential disulfide cleavage followed by the nucleophilic attack of the sulfide on the activated carboxylic acid. Then a Staudinger intramolecular reduction takes place to form the iminophosphorane intermediate **10**. Finally, the aza-Wittig reaction takes place, forming the thiazoline (Scheme 6).

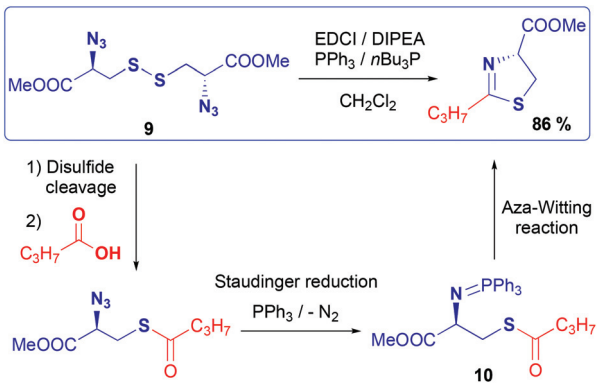
Recently, Chen *et al.* disclosed the use of benzylamidines **11** with 2-aminothiol to form thiazolines through a catalytic condensation mediated by copper.[28] The authors found that using 0.2 eq. $CuBr_2$ under solvent-free conditions made it possible to obtain 2-thiazoline in 75% yield (Scheme 7).



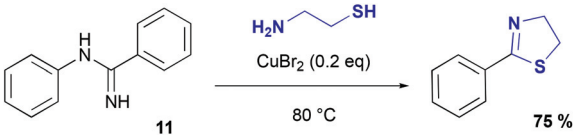
Scheme 5 Synthesis of 2-thiazolines using the Hendrickson reagent.[26]



Scheme 3 Proposed pathway for obtaining 4-Br-2-phenylthiazoline using 1 eq. of Na_2CO_3.[16]



Scheme 6 Proposed pathway for the synthesis of 2-thiazolines using **9**.[27]



Scheme 7 $CuBr_2$ catalyzes the addition of aminothiol to benzyl amidine.[28]

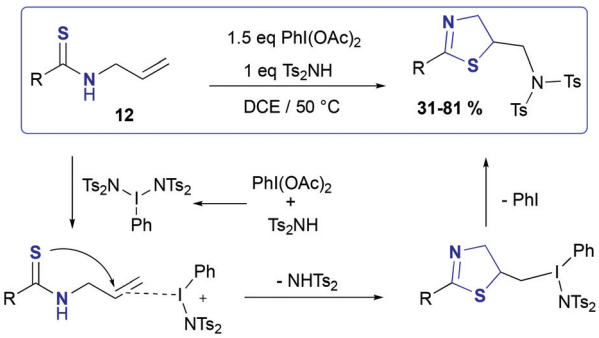
2.3. From thioamides not derived from amino alcohols

Until 2009, only two general methods were known for the synthesis of 2-thiazolines. However, in the last ten years, chemists have developed new synthetic routes to access 4- or 5-substituted thiazolines, avoiding the use of aminothiols or amino alcohols as starting materials.

To achieve this, most of these reports use simple thioamides as raw materials to form *N*-vinyl or *S*-vinyl derivatives. Then in a second step, the vinyl group is activated to trigger a 5-*exo-trig* cyclization and the corresponding 2-thiazoline is obtained. Other examples make use of activators, located at the β position to the N or S atom of the thioamide (N or S β-activation), to produce the heterocycle *via* a 5-*exo-tet* cyclization. Thus, when the S atom is functionalized, the 4-substituted thiazoline is formed, while the functionalization of the N atom provides the 5-substituted thiazoline (Scheme 8).

Examples related to *N*-vinyl activation of thioamides are as follows. The hypervalent iodine oxidant has served to activate the vinyl moiety in thioamides **12** to get 5-substituted 2-thiazolines *via* a 5-*exo-trig* cyclization.[29] The authors accomplished the synthesis of thiazolines using Ts_2NH and $PhI(OAc)_2$. The proposed pathway proceeds through the *in situ* formation of the hypervalent iodine species $PhI(NTs_2)_2$, which activates the double bond and makes it susceptible to a nucleophilic attack (Scheme 9).

In 2015, using an outstanding photocatalytic method,[30] Nicewicz and Morse developed a methodology to obtain 5-substituted 2-thiazolines using the organic photoredox catalyst **13** and different vinyl thioamides.[31] The reaction proceeds with 2.5 mol% of **13**, diphenyl disulfide, using a 450 nm LED. The

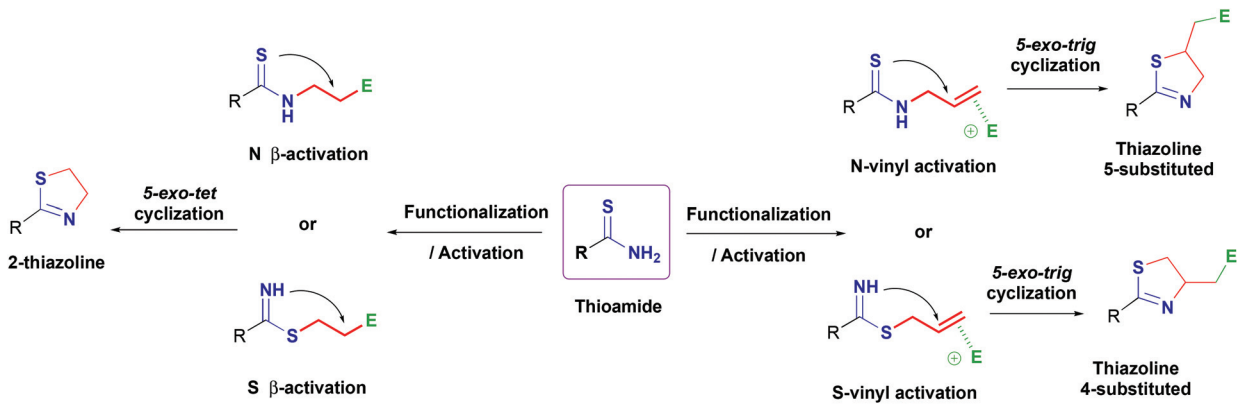


Scheme 9 Hypervalent iodine as an activator of vinyl thioamides.[29]

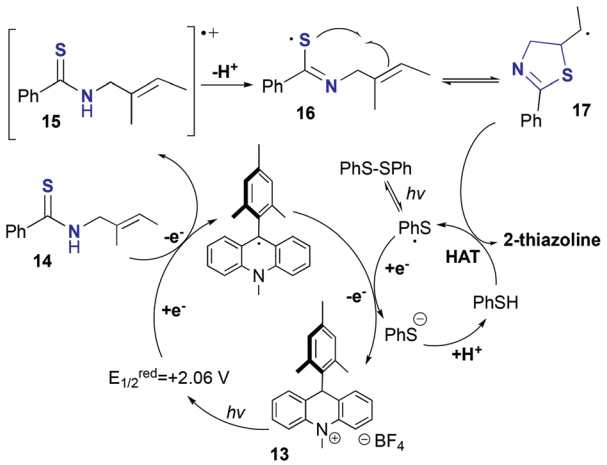
authors proposed that acridinium **13** is transformed into its highly excited state ($E^{red}_{1/2}$ = +2.06), which accepts an electron from thioamide **14** to form **15**. This compound can lose a proton, leading to radical **16** that cyclizes into the radical-thiazoline **17**. Then a hydrogen atom transfer (HAT) occurs to produce the final product and the thiyl radical. This latter can be formed after the *hv* excitation of the phenyl disulfide, which reacts with the acridine radical to regenerate the catalyst (Scheme 10).

Similarly, *N*-vinylthioamides can be cyclized using electrochemical synthesis to give CN-containing 2-thiazolines **18**.[32] This 5-*exo-trig* cyclization could be achieved using NH_4SCN as the double bond activator and supporting electrolyte. Using a graphite rod as both the anode and cathode in CH_3CN at 2.0 V, the authors obtained the desired thiazoline in 85% yield. Based on the oxidation peaks in cyclic voltammetry, the authors proposed that the SCN anion generates the $(SCN)_2$ species in the anode. Then the thioamide reacts with SCN^-, leading to *N*-vinyl activation *via* intermediate **A**, which allows an intramolecular nucleophilic attack to produce thiazoline **18**, while the resulting proton is reduced to hydrogen at the cathode (Scheme 11).

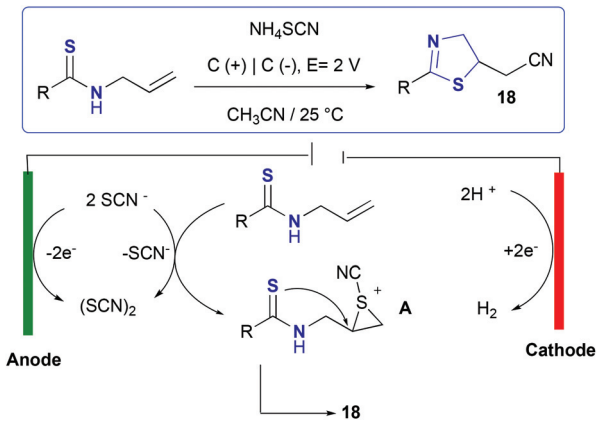
Not only thioamides can be used to produce 2-thiazolines through *N*-vinyl activation, carbamodithionates or thioureas can be used as well. For example, *N*-allylcarbamodithionates



Scheme 8 The general model of the functionalization–activation of thioamides.



Scheme 10 Synthesis of 2-thiazolines by photocatalysis.[30]

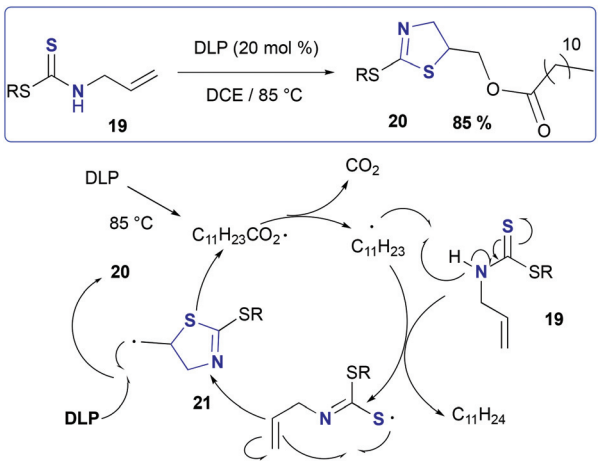


Scheme 11 Electrochemical synthesis to get 2-thiazolines.[32]

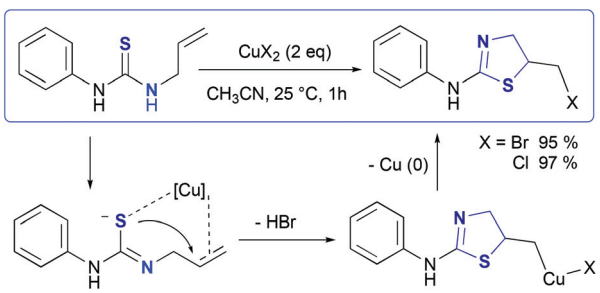
19 can produce 5-substituted thiazolines in a tandem radical reaction.[33] The authors studied the cyclization of **19** using 20 mol% dilauroyl peroxide (DLP) as a catalyst, affording thiazoline **20** in 85% yield. They proposed that DLP dissociates under the heating conditions to produce lauryl radicals, which can lose CO_2, affording undecyl radicals. Then, this radical can take a proton from **19** to generate the thiyl radical and promote the 5-*exo-trig* cyclization. The radical-intermediate **21** reacts under a radical substitution with DLP, leading to the final product and the starting lauroyl radical (Scheme 12).

Likewise, Rai and Maddani reported the synthesis of 5-bromo and 5-chloromethyl 2-amino thiazolines in excellent yields, using $CuBr_2$ or $CuCl_2$ with *N*-allylthioureas as starting materials.[34] The authors proposed the formation of a copper complex between the sulfur atom and the alkene moiety to activate the *N*-vinyl moiety, then a nucleophilic attack and a reductive elimination reaction produce the thiazoline (Scheme 13).

On the other hand, an example of *S*-vinyl activation of thioamides to afford 4-substituted thiazolines was reported by



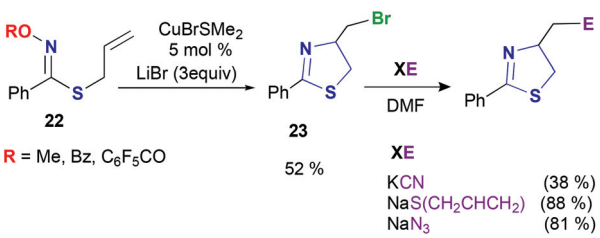
Scheme 12 The mechanism of *N*-vinyl activation of *N*-allylcarbamodithionates.[33]



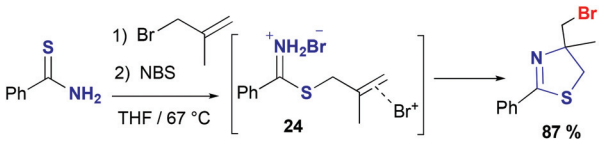
Scheme 13 $CuBr_2$ or $CuCl_2$ as activators of *N*-allylthioureas.[34]

Lemercier and Pierce.[35] They used thiohydroximic acids **22** to transform them into thiazolines **23**, using CuBr·SMe_2 as a catalyst. To do that, N–O bond activating groups such as Me-, Bz-, and pentafluorobenzoyl-substituted groups were used. The pentafluorobenzoyl-substituted group achieved the best result, affording **23** in 52% yield (Scheme 14). An interesting feature of this work was the feasibility of the functionalization of the bromine atom into different functional groups such as nitrile, thioallyl, and azide, thus demonstrating the potential scope of this reaction.

Following the last work, the same research group reported the use of *S*-allyl thioamides **24**, analogous to **22**, to get 2-thiazolines 4-substituted *via* an *S*-vinyl activation using NBS as



Scheme 14 Synthesis of 2-thiazoline **23** and its functionalization.[35]



Scheme 15 NBS as an activator of *S*-allyl thioamides **24**.[36]

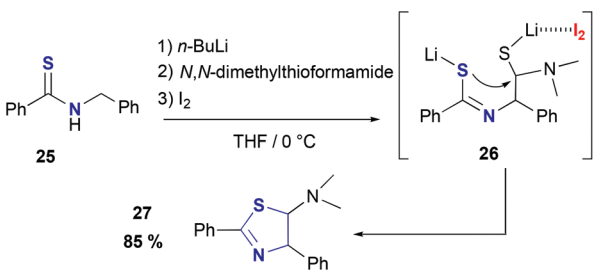
the activator (Scheme 15).[36] Thereafter, this methodology was extended to its chiral version, using $(DHQD)_2PHAL$ as a catalyst.

On the other hand, Murai *et al.* explored the N β-activation of thioamides as a strategy to obtain 5-amino thiazolines using thioamides **25**.[37] When they reacted this compound with 2 eq. of *n*-BuLi, *N*,*N*-dimethylthioformamide, and I_2, they were able to obtain 5-amino-2-thiazoline **27** in 85% yield. The I_2 ensures that the LiS group in **26** behaves as a better leaving group, facilitating the 5-*exo*-*tet* cyclization (Scheme 16).

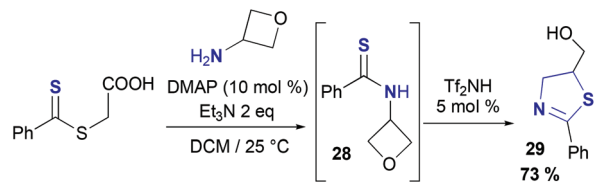
Another example involves the use of *N*-thioacetyloxetane **28** as the intermediate with 5 mol% of $NHTf_2$ that promotes the N β-activation to get thiazoline **29** in 73% yield (Scheme 17).[38]

Likewise, examples of the S β-activation of thioamides can be found in the literature. For instance, in 2011, Pathak *et al.* disclosed an organic solvent-free method where thioamides in combination with 2-bromo-ethylamine **30** provide the corresponding 2-thiazoline in 91% yield.[39] The authors proposed an *S*-alkylation as the first step to afford **31**. Once the β position to the S atom is activated by the ammonium salt, **31** is deprotonated by water to allow an intramolecular-nucleophilic attack (Scheme 18).

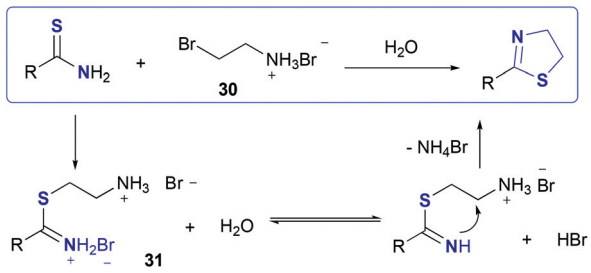
Similar reports where the reaction proceeds *via* an S β-activation were independently published almost at the same time by Alsharif[40] and Parker[41]. Both showed the possibility to obtain 2-thiazolines using ethyl 4-bromocrotonate **32**. Alsharif



Scheme 16 I_2 as an activator of thioamides.



Scheme 17 $NHTf_2$ as an activator of *N*-thioacetyloxetane.[38]



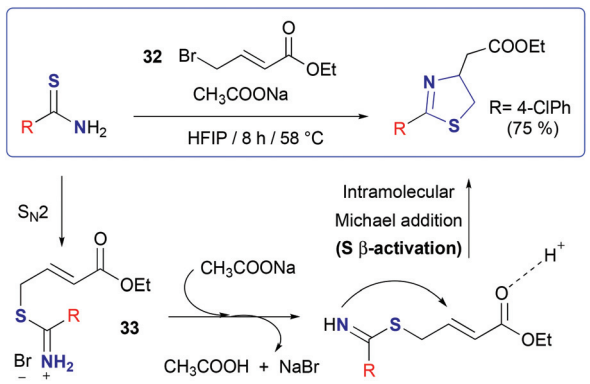
Scheme 18 2-Bromo-ethylamine bromo hydrate **30** used to activate thioamides.[39]

used hexafluoroisopropanol (HFIP) as a solvent in the reaction between thioamides and **32**, providing the thiazoline in 75% yield. This methodology can be extended to *N*-phenylthioureas and thiosemicarbazones as precursors (Scheme 19).[42]

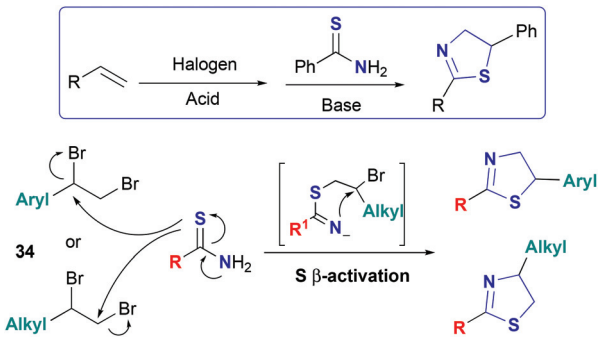
A few months later, Parker *et al.* reported a similar strategy, improving this method using other solvents in high concentration conditions.[41] The pathway proposed by the authors proceeds *via* an S_N2 substitution between the thioamide and **32**. After intermediate **33** reacts with the base, the ester moiety is protonated, favoring an intramolecular Michael addition (Scheme 19).

An alternative method for accessing 5- or 4-substituted 2-thiazolines *via* an S β-activation involves the *in situ* formation of 1,2-dibromoalkanes **34** using alkenes, LiBr, and UHP, which under a nucleophilic addition of the thioamide in soft basic conditions affords the desired product (Scheme 20).[43] Regarding regioselectivity, the authors explain that the external C–Br bond in alkyl intermediates is more electrophilic than the internal one, providing 4-substituted 2-thiazolines, while the internal C–Br bond in styrene tends to be most electrophilic to the addition of the thioamide, providing 5-substituted 2-thiazolines.

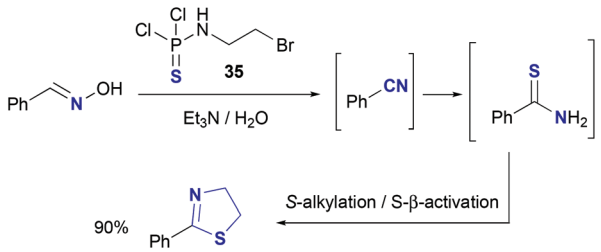
Finally, 2-thiazolines can be synthesized from dichlorothiophosphoramidate **35** in combination with aldoximes, nitriles, or carboxylic acids.[44] **35** was mixed with phenylaldoxime and Et_3N to obtain 2-phenyl thiazoline in 90% yield, using water as a promoter. The experimental evidence suggests that **35** dehy-



Scheme 19 Synthesis of 2-thiazolines using 4-bromocrotonate **32**.[41]



Scheme 20 Activation of alkenes *via* a one-pot reaction using thioamides.



Scheme 21 Dichlorothiophosphoramidate **35** used to get 2-thiazolines.[44]

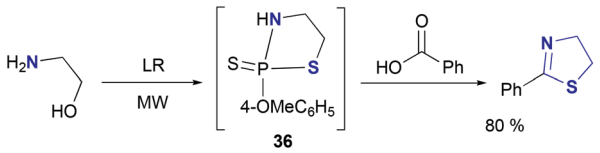
drates the aldoxime to form the corresponding nitrile, which is transformed into the thioamide to finally produce the desired thiazoline through an *S*-alkylation and a subsequent S-β-activation (Scheme 21).

2.4. Recent methodologies using amino alcohols

The use of amino alcohols in the synthesis of 2-thiazolines is the method that has been explored more, owing to the widely available commercial amino alcohols that are used as starting materials. This methodology involves the *N*-acylation of the amino alcohol to obtain the *N*-(hydroxy)amide, which can be transformed into the *N*-(hydroxy)thioamide using thionation agents and finally, intramolecular cyclization provides the desired product.

In the last ten years, interesting methods have been developed using this general synthetic route. In 2008, Seijas *et al.* showed the possibility to get 2-phenyl thiazolines in 80% yield using benzoic acid, 2-aminoethanol, and Lawesson's reagent (LR) by irradiation with microwaves under solventless conditions.[45] The hydroxyl group in the amino alcohol is replaced by the thiol group in the presence of LR. Then another molecule of LR produces species **36**, which activates the carboxylic acid, facilitating the formation of the desired product (Scheme 22).

As we mentioned above, the final step in the synthesis of 2-thiazolines using amino alcohols is the activation of the hydroxyl group. The most useful activating reagents are MsCl, TsCl, Burgess reagent, DAST, Mitsunobu conditions, and



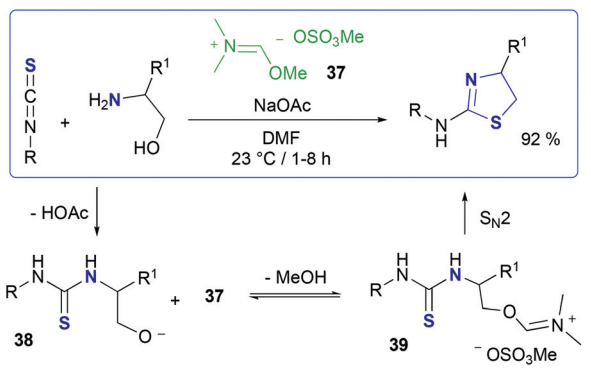
Scheme 22 Synthesis of 2-thiazolines using RL under microwave irradiation.[45]

Deoxo-Fluor, or the most recent ones disclosed: P_2S_5,[46] Ph_3PO/Tf_2O,[47] fluoroalkanosulfonyl fluorides,[48] PPE,[49] and XtalFluor-E.[50]

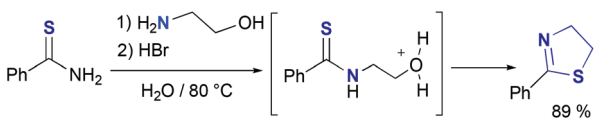
Pursuing the development of new efficient reagents to carry out this final cyclization, the use of a Vilsmeier reagent **37** was considered to promote alcohol activation.[51] Using NaOAc, **37**, and isothiocyanates, the *N*-phenyl 2-amino thiazoline is formed in 92% yield. Thiourea **38** is obtained after the nucleophilic attack of the isothiocyanate on the amino alcohol. Then **38** reacts with **37** through the hydroxyl group to form **39**. Finally, an intramolecular S_N2 reaction affords the 2-thiazoline and MeOH that regenerate sulfate **37** (Scheme 23).

On the other hand, a green method reported in 2015 by Pathak showed the feasibility to obtain 2-thiazolines *via* the formation of β-hydroxythioamides, using amino alcohols and thioamides. The reaction is promoted using HBr to protonate the hydroxyl group and facilitate the nucleophilic attack on the sulfur atom (Scheme 24).[52]

Until now, we have shown several methods for the synthesis of 2-phenyl, heteroaryl, or alkyl thiazolines. However, there are only a few reports concerning the synthesis of ferrocenyl thiazolines. As is well known, ferrocene derivatives are important compounds in many areas of chemistry.[53] Molina and



Scheme 23 The mechanism to get 2-thiazolines using **37** and isothiocyanates.[51]



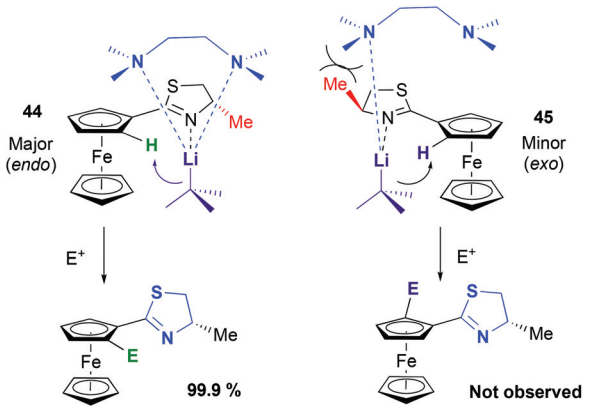
Scheme 24 HBr as a dehydrating agent.[52]

Tárraga[54] and two years later Bernardi and Bonini[55] disclosed the first methods to obtain 5-ferrocenyl thiazolines. Even these reports show the possibility to introduce a ferrocenyl moiety into the thiazoline core, and the position of ferrocene is not the best to exploit its use as a bidentate ligand. As in their analogues, 2-ferrocenyl oxazolines or 2-ferrocenyl imidazolines,[56] the 2-thiazoline fragment can be used as an *ortho*-directed metalation group (DMG) to produce 1,2-disubstituted ferrocenes, which are important intermediates in the synthesis of ligands with planar chirality.[57]

With regard to this, the first synthetic method for the synthesis of 2-ferrocenyl thiazolines was reported by López-Cortés *et al.*[58] In this work, the Fischer aminocarbene complex **40** was transformed into chromium ferrocenylaminocarbene **41** using ethanolamine.

Then, **41** is converted to ferrocenylthioamide **44** *via* a sulfurative demetalation reaction. Finally, the cyclization of **42** using MsCl provides the desired thiazoline in 94% overall yield (Scheme 25).[58]

These 2-ferrocenyl thiazolines were investigated as a directed metalation group (DMG) to obtain 1,2-disubstituted ferrocenes. Using *t*-BuLi and TMEDA, the selectivity obtained was more than 99.9%. The authors explain, based on DFT calculations, that the *endo* transition state **44** is less energetic than the *exo* analogous **45** because the TMEDA interacts with the methyl group, forcing the formation of only the *endo* transition state (Scheme 26).



Scheme 26 2-Thiazolines used as a DMG in ferrocene.[58b]

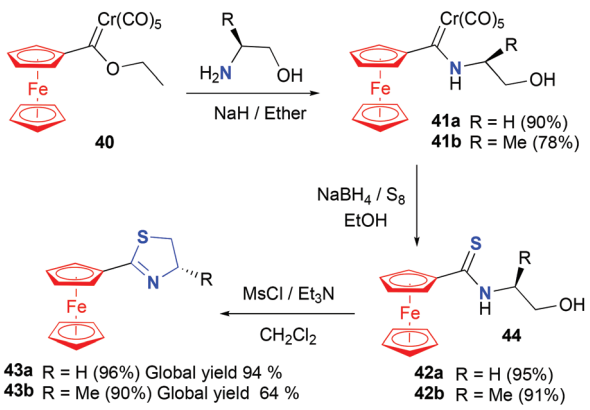
3. 2-Thiazolines as substrates in catalysis

Thiazolines can undergo different reactions such as oxidation, reduction, or hydrolysis. Among all these reactions, the hydrolysis of 2-thiazolines to obtain α-alkyl cysteines has attracted the attention of chemists due to the importance of these modified amino acids to build or modify peptides and proteins.[59] The general method is based on the reaction of a stabilized anion at the 4-position by an electron-withdrawing group with an alkyl halide. Once the thiazoline 4,4-disubstituted compound is obtained, it can be transformed into the cysteine derivative by an acid hydrolysis reaction. Nevertheless, the principal disadvantage of this method is the lack of enantioselectivity.

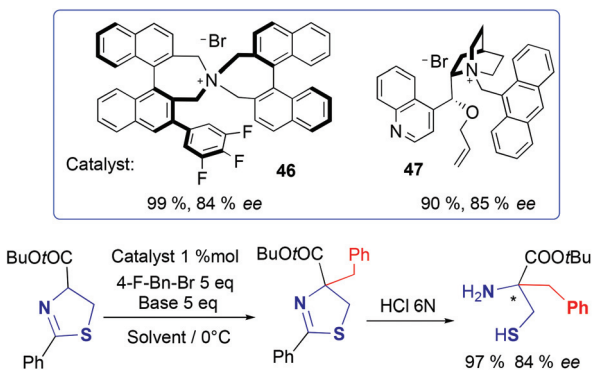
To overcome this inconvenience, methods in asymmetric catalysis have been developed. The first approximation was published by Kim and Jew in 2006.[60] This method involves a phase-transfer catalytic alkylation (PTA). 1 mol% of the catalyst **46** or **47** with 5 eq. of alkyl halide and 5 eq. of a base provided the desired product with high enantioselectivities of 84% and 85% ee. These new 4,4-disubstituted thiazolines were transformed to the α-alkyl cysteines *via* hydrolysis using 6 N HCl (Scheme 27).

Similarly, these thiazolines have been used in the asymmetric 1,4-addition reaction towards methyl acrylate, promoted by $Ca(OiPr)_2$ using 10 mol% of ligand **48**. Thus, the 4,4-disubstituted thiazoline was obtained in 83% yield and 86% ee. A similar result was found with ligand **49** (Scheme 28).[61]

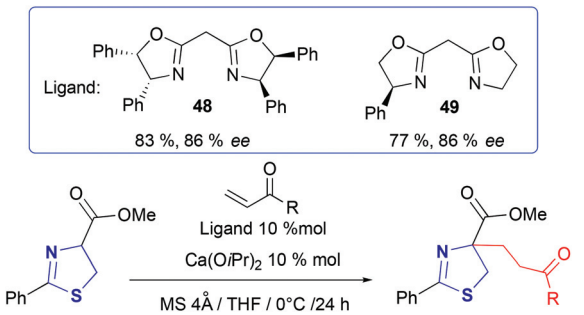
In a plausible mechanism, the catalytic species **50** facilitates the thiazoline deprotonation leading to the enolate **51** and 2-propanol. Then, 1,4-addition is carried out and the resulting intermediate **52** could be protonated by two different



Scheme 25 The methodology to get 2-ferrocenyl-2-thiazolines.[58]



Scheme 27 Synthesis of α-alkyl cysteines *via* a 2-thiazoline functionalization.[60]

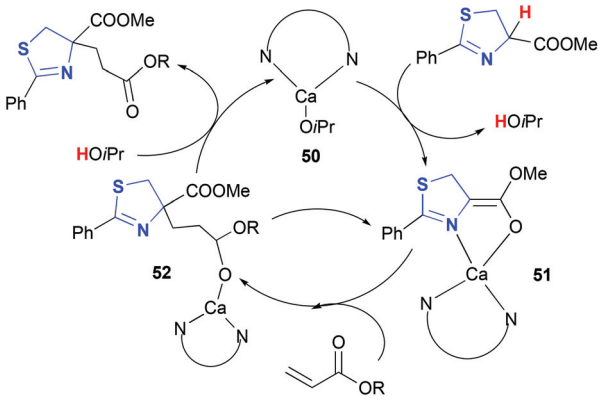


Scheme 28 2-Thiazolines as substrates in an asymmetric 1,4-addition reaction.[61]

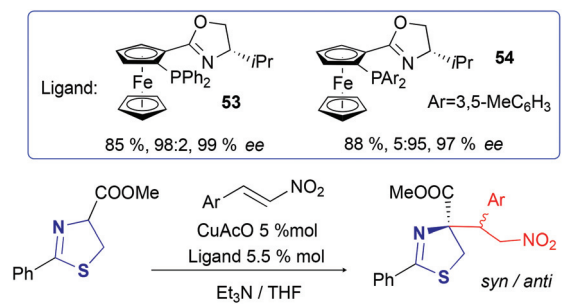
pathways. The first one through protonation by 2-propanol and the second pathway *via* interaction with another thiazoline to regenerate **51** and release the product (Scheme 29).

The Michael addition of 2-thiazolines-4-carboxylates esters to nitro alkenes has been also studied in catalysis.[62] This reaction was catalyzed using 5 mol% of CuOAc with the Fc–PHOX ligands **53** and **54**. For example, the use of **53** leads a 92 : 8 (*syn* : *anti*) ratio and 99% ee. The reaction scope included different nitroalkenes, providing excellent ee (Scheme 30).

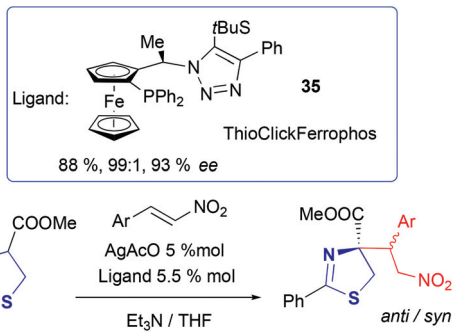
One year later, Fukuzawa *et al.* reported the use of Ag instead of Cu in the same reaction.[63] In this case, they



Scheme 29 The mechanism of 2-thiazolines as substrates in the asymmetric 1,4-addition reaction.[61]



Scheme 30 Michael addition of 2-thiazolines to nitroalkenes using Cu.[62]



Scheme 31 Michael addition of 2-thiazolines to nitro alkenes using Ag.[63]

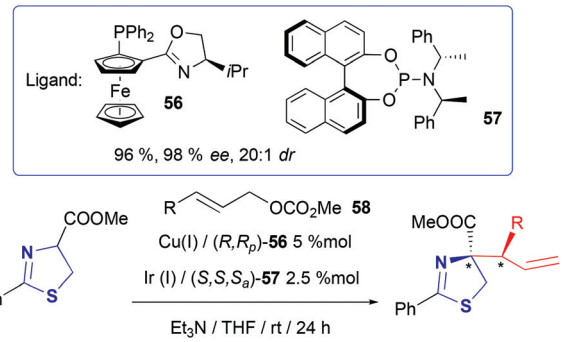
observed that ThioClickFerrophos **55** was produced with high ee and preference for the *anti*-diastereomer. The authors used different aryl nitroalkenes to study the scope of the reaction. All substrates showed excellent selectivity toward the *anti*-diastereomer, with ee values above 90% (Scheme 31).

The most recent report concerning the functionalization of 2-thiazolines-4-carboxylates was reported by Wu and Wang. They used bimetallic synergistic catalysis[64] to obtain α-alkyl cysteine precursors in an asymmetric allylic alkylation reaction.[65]

The system Cu/Ir was used in combination with two different ligands: the Fc–PHOX ligand **56** and Feringa's phosphoramidite ligand **57**. Phenyl cinnamyl carbonate **58** and the 2-thiazoline were reacted in the presence of NEt_3, affording the product in 96% yield, 98% ee, and 20 : 1 dr. Then different cinnamyl carbonates were tested to study the scope of this reaction, and excellent selectivities and conversions were achieved (Scheme 32).

4. Metal-catalyzed reactions using 2-thiazoline ligands

Since the first example published by Helchem in 1991[66] concerning the use of C_2-symmetric bis(thiazolines) on Rh-cata-



Scheme 32 Functionalization of 2-thiazolines *via* bimetallic synergistic catalysis.[64]

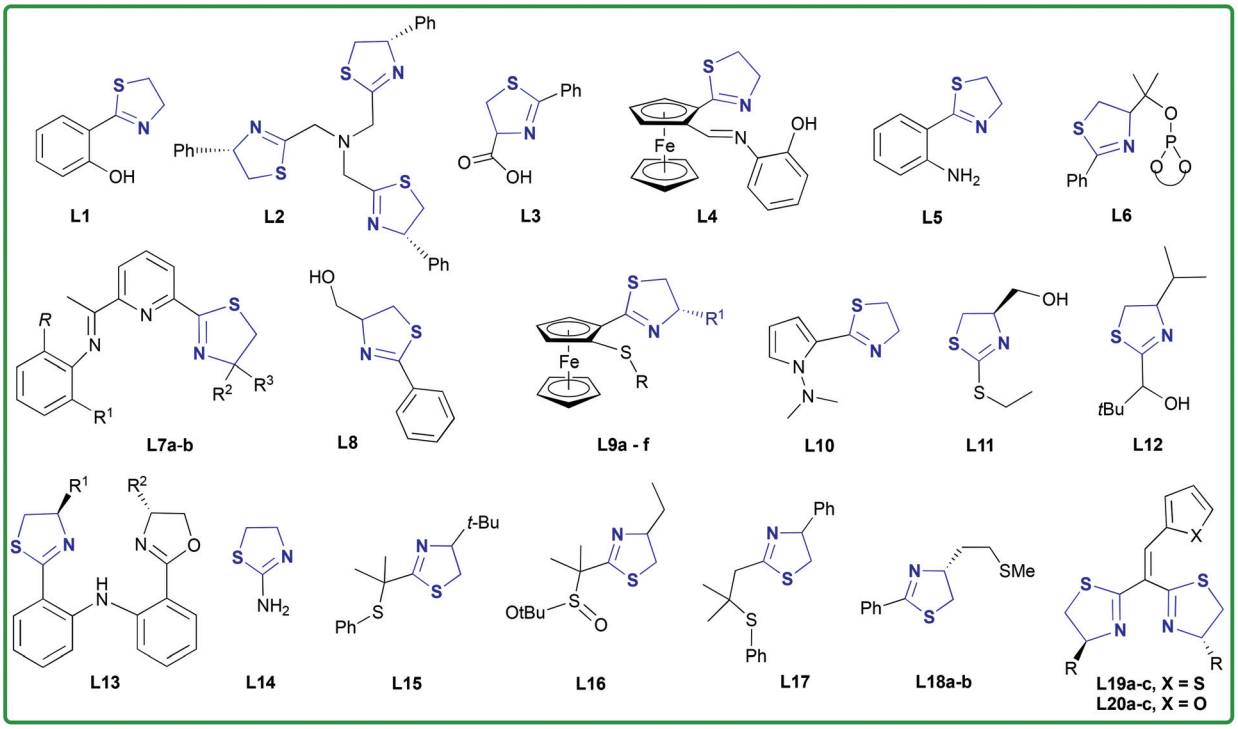


Fig. 1 Ligands used in metal-catalyzed reactions.

lyzed hydrosilylation of ketones, comparative catalytic studies have brought out big differences between the oxazoline and thiazoline ligands. The electronic and steric effects, resulting from the substitution of oxygen by sulfur, lead to different behaviors with regard to the chelation of metals. While oxazolines coordinate exclusively *via* the nitrogen atom to the metal, S coordination is also possible with thiazolines, especially in reactions involving late transition metals.

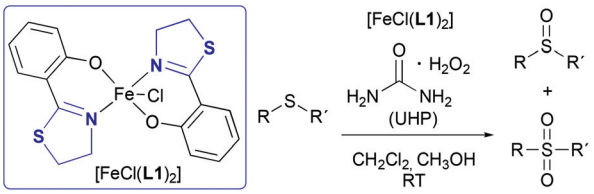
At the beginning of the 21st century, thiazoline ligands have been mentioned in three reviews, two devoted to sulfur-containing ligands[67] and another focusing on 2-thiazolines.[7] The real interest in this family of ligands has continued with the synthesis of several new 2-thiazoline ligands and the study of their catalytic properties in numerous reactions. The main 2-thiazolines used as ligands are shown in Fig. 1. Most of them are analogues of the well-known oxazolines. In this section, we will review the involvement of 2-thiazolines as ligands in organometallic catalysis, focusing on those, which have been published since the end of 2007.

4.1. Sulfide oxidation

Amini *et al.* reported the first catalytic activity of a thiazoline–Fe(III) complex in oxidation reactions (Table 2).[68] **L1** acts as a bidentate O–N donor ligand. The isolated air-stable Fe complex proved to be efficient for the oxidation of a series of structurally diverse sulfides. The catalytic oxidation was performed under mild conditions using a urea hydrogen peroxide (UHP) adduct as a green oxidant. The conversions of substrates, in the range of 49–97%, depend on the nature of the sulfide (TON = 11.4–18.2).

Aromatic sulfides undergo oxidation reactions more easily than aliphatic substrates. In all cases, high selectivity toward sulfoxide was observed (81 to 100%).

Table 2 Oxidation of sulfides catalyzed by the Fe(III) complex of thiazoline **L1**[a,68]



Entry	Substrate	Conversion[b] (TON)	Selectivity toward sulfoxide[c]
1	Ph–S–CH_3	91 (18.2)	86
2	Ph–S–Et	87 (17.4)	85
3	Ph–S–CH_2–Ph	95 (19)	88
4	Ph–CH_2–S–CH_2–Ph	97 (19.4)	81
5	Ph–S–Ph	82 (16.4)	88
6	Et–S–Et	61 (12.2)	100
7	Bu–S–Bu	55 (11)	100
8	C_8H_{17}–S–C_8H_{17}	49 (9.8)	100

[a] Reactions were performed with the molar ratios for $[Fe(\mathbf{L1})_2]Cl$/UHP : substrate : oxidant are 1 : 20 : 40 in a 1 : 1 mixture of CH_2Cl_2/CH_3OH in air at RT within 15 min. [b] Conversion = [(mmol of sulfoxide + mmol of sulfone)/mmol of catalyst]. [c] Selectivity = [sulfoxide%/(sulfoxide% + sulfone%)] × 100.

4.2. Asymmetric allylic oxidation

Very recently, Fu *et al.* published the synthesis of a novel series of C_3 symmetric tris(thiazoline) ligands **L2** and their applications in the asymmetric Cu-catalyzed allylic oxidation of cyclopentene and cyclohexene compounds.[69] In the allylic oxidation of cyclopentene with *t*-butyl perbenzoate as the oxidant, the **L2**/Cu(OTf)$_2$ system showed low catalytic activity for the formation of the desired cyclopentene product (Scheme 33). The Cu(II)-**L2** system showed a better catalytic activity for the allylic oxidation of cyclohexene (87% yield) but with lower enantioselectivities (35% ee).

4.3. Transfer hydrogenation

The group of Denizalti showed that the thiazoline carboxylic acid ligand **L3** acts as an N,O ligand towards the Ru(II) center.[70] From this ligand, a piano-stool ([RuCl(*p*-cymene)**L3**]) was prepared and applied for the first time in the transfer hydrogenation reaction of various carbonyl compounds.

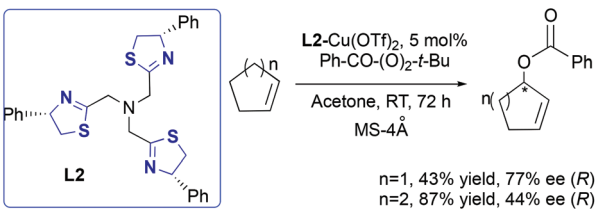
This complex efficiently performed the transformation of a whole range of substrates (aromatic ketones, heterocyclic ketones, tetralone, cyclic, or acyl aliphatic ketones as well as benzaldehyde) in high yields (82–99%) (Scheme 34).

Recently, Lopez-Cortés *et al.* designed a new [N,N,O]-tridentate Schiff base ligand **L4** using 2-ferrocenyl-2-thiazoline as a scaffold.[71] **L4** was coordinated with [RuCl$_2$(PPh$_3$)$_3$] to study its role in the transfer hydrogenation of ketones. The preformed ruthenium complex of **L4** proved to be active, giving good to excellent conversions in the transfer hydrogenation of some aryl and alkyl ketones under the optimized catalytic conditions. In particular, *para*- or *meta*-methyl groups and *para*- or *meta*-substituted ketones with moderate to strong electron-withdrawing groups such as –Cl, –Br, –CN, and –NO$_2$, show good to excellent conversions (71–99%) (Fig. 2). Note that the phosphine-free **L4**-Ru system displayed a good catalytic performance compared with other ruthenium catalytic systems containing the [P,N,P]- and [P,N,O]-tridentate ligands.

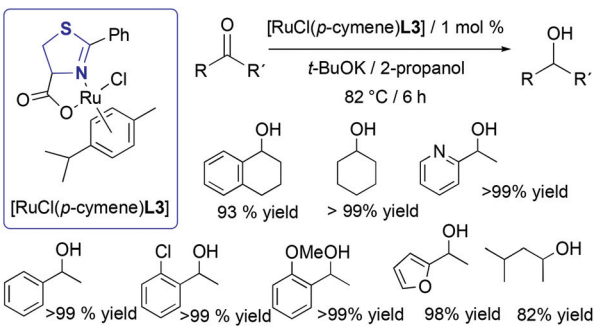
4.4. Hydrogenation

Recently, Suresh *et al.* used the 2-aniline–thiazoline ligand **L5** to functionalize the periodic mesoporous organosilica and support palladium nanoparticles (Scheme 35).[72] This heterogeneous catalyst showed good efficiency toward hydrogenation reactions of industrially important compounds such as styrene oxide, 2-furfuraldehyde, and nitrobenzene. The complete conversion of styrene epoxide was achieved with high selectivity at room temperature in H$_2$O under 300 psi of hydrogen gas.

This heterogeneous Pd-catalyst exhibits good recyclability with high selectivity. Five consecutive hydrogenations of styrene oxide were carried out with the recycled catalyst without any significant decrease in the yield. Under the same



Scheme 33 Asymmetric catalytic allylic oxidation of cyclopentene or cyclohexene catalyzed by **L2**/Cu(OTf)$_2$.[69]



Scheme 34 Transfer hydrogenation catalyzed by the Ru(II) complex of thiazoline **L3**.[70]

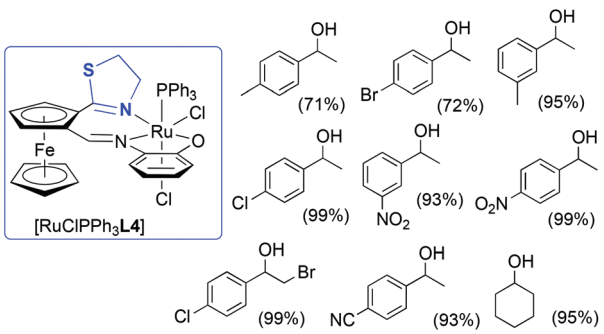
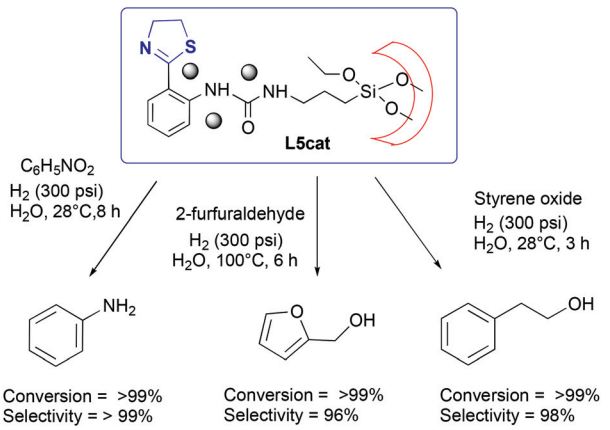


Fig. 2 Selected results for transfer hydrogenation catalyzed by the ruthenium complex of **L4** using 0.75% of complex, 1.2 eq. of KOH, in 2-propanol for 6 h at 80 °C.[71]



Scheme 35 Pd nanoparticles incorporated on thiazoline **L5** derived mesoporous silica catalyzed hydrogenation of styrene epoxide, furfural, and nitrobenzene.[72]

reaction conditions, excellent results were obtained for the hydrogenation of 2-furfuraldehyde and nitrobenzene.

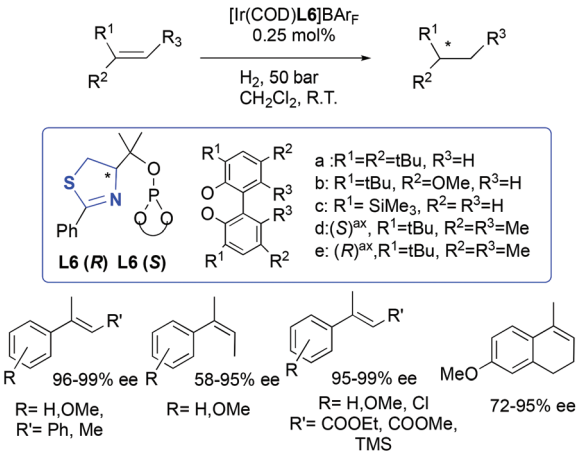
Diéguez *et al.*[73] designed new thiazoline ligands **L6** containing a biaryl phosphite fragment and demonstrated their potential in Ir-catalyzed hydrogenation reaction of various prochiral trisubstituted olefins and 1,1-disubstituted terminal olefins (Scheme 36). Excellent activities and enantioselectivities (up to 99%) were obtained for *E*-trisubstituted olefins. Bulky trimethylsilyl groups contained in the biaryl phosphite moiety provided the best enantioselectivity. Selectivity is controlled by the configuration of the alkyl backbone and not by the configuration of the aryl group on the phosphite.

The asymmetric hydrogenation of the more demanding *Z* isomers was efficiently achieved with improved enantioselectivities. In this case, the enantioselectivities were affected by both the substituents and the configuration of the biaryl phosphite moiety.

In addition, the iridium complexes of **L6** proved to be efficient catalysts for the reduction of trisubstituted alkenes such as α,β-unsaturated ketones, allylic alcohol, and allylic acetate, and α,β-unsaturated esters, and vinylsilane. Again, excellent enantioselectivities were obtained in both enantiomers of the reduction products (94–99% ee).

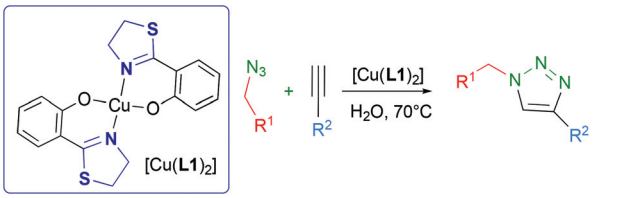
4.5. Cycloaddition

The group of Amini extended the use of **L1** to the Cu-catalyzed Huisgen cycloaddition of organic azides with alkynes.[74] An isolated air-stable Cu complex catalyzes the [3 + 2] cycloaddition of diverse terminal alkynes with benzyl azide, affording the expected product in high yield (90 to 97%). The incorporation of electron-withdrawing and electron-donating groups on the phenyl ring in the substrates did not have any remarkable influence on this reaction (Table 3). It is interesting to note that the Cu(II) complex of thiazoline **L1** can efficiently produce in one pot conditions the corresponding triazole by the cycloaddition of a wide range of diversely substituted phenyl acetylenes with a mixture of benzyl chlorides (or bromides). The



Scheme 36 Ir-Catalyzed asymmetric hydrogenation of *E*- and *Z*-trisubstituted olefins using **L6**.[73]

Table 3 Cycloaddition of alkyl azides with terminal alkynes in the presence of [Cu(**L1**)$_2$][74]



Entry	R^1	R^2	Yield (%)
1	$PhCH_2$–	Ph	97
2	*p*Me–$PhCH_2$–	Ph	94
3	*p*NO_2–$PhCH_2$–	Ph	92
4	$PhCH_2$–	*p*MeO–Ph	93
5	$PhCH_2$–	*p*MePh	90
6[a]	Ph	Ph	96
7[b]	Ph	Ph	79

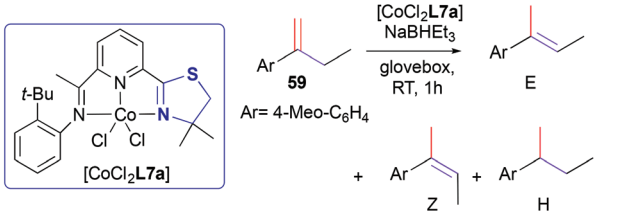
[a] Reaction carried out using benzyl chloride in the presence of sodium azide. [b] Reaction carried out using benzyl bromide in the presence of sodium azide.

reaction works better using benzyl chloride than benzyl bromide (Table 3, entries 6 and 7).

4.6. Isomerization of simple α-alkyl styrene

Lu *et al.* have demonstrated the excellent performance of the thiazoline iminopyridine ligand **L7a** in the cobalt-catalyzed isomerization of various α-alkylstyrene.[75] For example, the isomerization of (but-1-en-2-yl)-4-methoxybenzene **59** was performed at room temperature using only 0.1 mol% catalyst load and $NaBHEt_3$ (3 mol%) as an activator to produce the *E* products with high selectivity (96%) (Table 4). The authors have described the isomerization of 25 substrates such as 1,1-disubstituted alkenes having electron-donating substituents as well as electron-withdrawing substituents on the phenyl group, monosubstituted alkenes, and 1,2-disubstituted alkenes, with high to excellent conversions (90 to 99%) and high selectivities toward *E* benzyl products (*E*/*Z* ratio between 18/1 and 20/1).

Table 4 Isomerization of (but-1-en-2-yl)-4-methoxybenzene catalysed by [$CoCl_2$**L7a**][75]



Entry	[$CoCl_2$**L7a**] (mol%)	*E*/*Z*/H (%)	Recovery
1	5	96/—/2	2
2	1	96/—/—	4
3	0.1	96/—/—	4

4.7. C–C and C–X coupling reactions

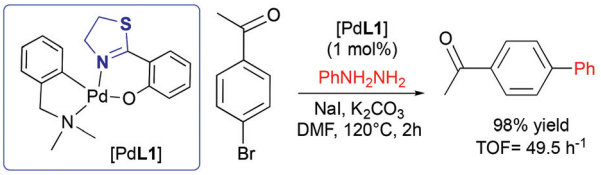
Suresh *et al.* synthesized palladium complexes using thiazoline **L1** and studied their performance in the cross-coupling reaction between 4-bromoacetophenone with phenylhydrazine (Scheme 37).[76] **L1** exhibited a high catalytic activity with a turnover frequency of 49.5 h^{-1} which is four times higher than that of other catalysts (TOF = 14.0 h^{-1}).[77] It tolerates electron-withdrawing, electron-donating, and electronically neutral aryl bromides, affording the coupled products in good to excellent yields. The cross-coupling reaction was also extended to 2-bromo pyridine, 1,3-dibromo benzene and 1,4-dibromo benzene.

The use of aryl chlorides has also been examined. Aryl chlorides with electron-withdrawing substituents react completely in a short time (2 h), while those with electron-releasing groups need a longer reaction time (20 h). In addition, a gram-scale reaction between 4-chlorobenzonitrile and phenylhydrazine took place under standard reaction conditions with excellent product yield (92%).

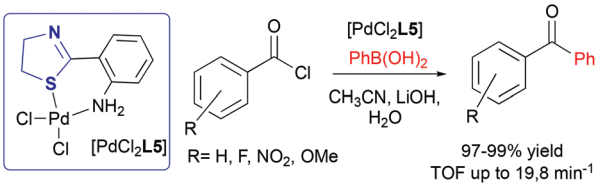
2-Aniline–thiazoline ligand **L5**[78] exhibits versatile coordination behavior with [$PdCl_2$(COD)] to afford three different complexes.[79] All these palladium complexes proved to be active in the cross-coupling reaction of phenylboronic acid with benzoyl chloride (Scheme 38). Among them, [$PdCl_2$**L5**] was the most efficient catalyst for carrying out these reactions under optimized conditions. It tolerates both electron-rich and electron-deficient benzoyl chloride derivatives and furnishes the desired products in excellent yields (97–99%). In addition, [$PdCl_2$**L5**] containing **L5** as the [N,S] ligand was an effective catalyst in the coupling reaction of terephthaloyl chloride with phenylboronic acid derivatives resulting in the desired bis-coupled product being formed in excellent yield (99%).

The palladium complex [$PdCl_2$**L5**] has also been an efficient catalyst for the Suzuki–Miyaura cross-coupling reaction between aryl bromide and phenylboronic acid under the optimized reaction conditions. 82 to 99% yields were obtained using a variety of aryl halides bearing electron-donating and/or electron-withdrawing substituents (Scheme 39a). Furthermore, [$PdCl_2$**L5**] could be used to perform one-pot coupling reactions using 4-bromobenzoyl chloride and phenylboronic acid (Scheme 39b). The expected product was obtained in 89% yield with a TOF of 0.64 min^{-1}.

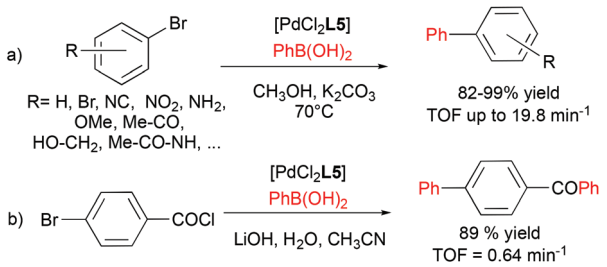
Recently, the same authors prepared **L5**-Pd nanoparticles to functionalize mesoporous silica. This material was used in the cross-coupling of aryl halides and acid chlorides with arylboronic acids.[80] Using the catalyst resulted in good to excellent yields irrespective of the electronic nature of aryl halides/acid chlorides and it also shows good recyclability (up to 5 cycles without affecting the yield in both reactions).



Scheme 37 Pd complexes bearing **L1** ligand catalyzed cross-coupling reaction of 4-bromoacetophenone with phenylhydrazine.[76]



Scheme 38 [$PdCl_2$**L5**] complex-mediated coupling reaction of acid chloride with arylboronic acids.[78,79]

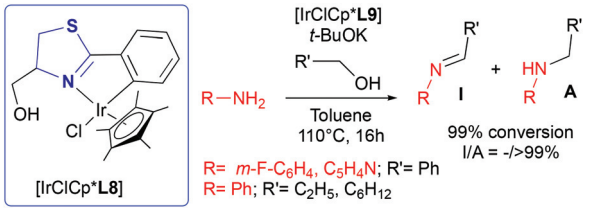


Scheme 39 (a) [$PdCl_2$**L5**] complex-mediated Suzuki–Miyaura cross-coupling reaction between aryl-bromide and phenylboronic acid. (b) One-pot coupling reaction of 4-bromobenzoyl chloride with phenylboronic acid catalyzed by [$PdCl_2$**L5**] complex.[78–80]

4.8. *N*-Alkylation of amines with alcohols

Denizalti *et al.* reported a new hydroxyl-thiazoline **L8** and two types of iridium(III) complexes.[81] The complex [IrClCp****L8**] was employed for the *N*-alkylation of a variety of amines (anilines bearing either electron-donating or electron-withdrawing groups, benzylamine, 2-naphthylamine, and 2-aminopyridine) with different alcohols (benzyl alcohol and aliphatic alcohols) with moderate to high activities and selectivities (Scheme 40).

The most significant results were obtained for the *N*-alkylation of 3-fluoropyridine and aminopyridine with benzyl alcohol and the *N*-alkylation of aniline with butanol or cyclohexanol (99% conversion, 99% selectivities for the secondary amine).



Scheme 40 Alkylation of amines with alcohols (selected results) catalyzed by the iridium(III) complex of thiazoline **L8**.[81]

[IrClCp*L8] was immobilized on multi-walled carbon nanotubes (MWCNTs–COOH) and tested for the alkylation of aniline with benzyl alcohol.

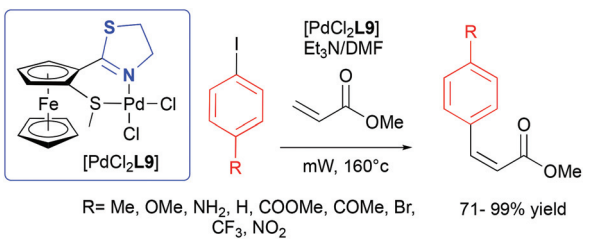
It was found that the immobilized iridium complex performed the transformation with an excellent conversion (99%) and high selectivity (I/A = 4/96) at low catalyst loading (≈0.3% of Ir). This supported complex can be recovered and reused three times with good conversions (99 to 96%).

4.9. The Mizoroki–Heck reaction

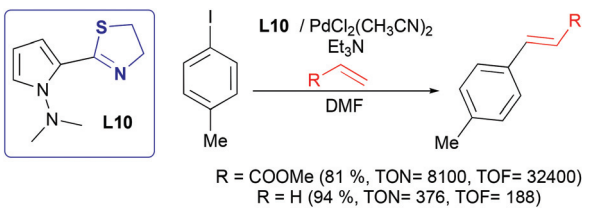
López-Cortés *et al.* synthesized 2-ferrocenyl-2-thiazolines **L9** bearing a thioether substituent in the ferrocene backbone, which act as an effective [N,S] bidentate ligand toward the palladium(II) center (Scheme 41).[58a] The Pd complex of **L9a** performed the cross-coupling between 4-iodotoluene and methyl acrylate under microwave irradiation. Under optimized conditions, the expected product was obtained in 96% yield with a TOF of 16 286 min^{-1}. This complex was more active than the related 2-ferrocenyl-2-oxazoline palladium complex (TOF = 10 364 min^{-1}). [$PdCl_2$**L9**] is also a convenient and highly efficient catalytic precursor for cross-coupling reactions of a wide range of activated and deactivated aryl iodides with methyl acrylate in short reaction times and excellent yields (92–99%).

On the other hand, a pyrrolic bidentate ligand with a 2-thiazoline fragment was used to catalyze the coupling between 4-iodotoluene and methyl acrylate.[82] The reaction was developed using microwave irradiation, using 0.5 mol% of ligand **L10** and [$PdCl_2(CH_3CN)_2$], in DMF and Et_3N, with the product obtained in a yield of 69% (Scheme 42). Upon decreasing the load of the ligand and the amount of Pd to 0.01%, a better result was observed, and the yield was 81%. Thus, the result of the coupling between iodotoluene and styrene was compared with that of the oxazoline analogue of **L10**, and it was observed that 0.1 mol% of oxazoline lead to 90% yield with a value of 900 for TON and TOF(h^{-1}). By doubling the reaction time, the values obtained using thiazoline slightly exceed the values obtained using oxazoline.

Finally, expanding the scope of this reaction, ethylene was used with iodotoluene, and a comparison of the results obtained using thiazoline and oxazoline again showed that the latter lead to better results.



Scheme 41 Mizoroki–Heck reaction of aryl iodides with methyl acrylate under microwave irradiation catalyzed by the palladium(II) complex of thiazoline **L9a**.[58a]



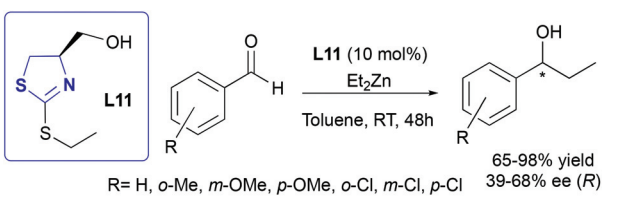
Scheme 42 Pyrrolic bidentate ligand **L10** used as a catalyst in the Mizoroki–Heck reaction of aryl iodides with methyl acrylate under microwave irradiation.[82]

4.10. Asymmetric addition of alkyl- and arylzinc compounds to aldehydes

Song reported new thiazoline based-N–O ligands containing chiral β-imino alcohols[83] and their application in the asymmetric addition of Et_2Zn to several aryl aldehydes. Among this series of ligands, the best performance in terms of enantioselectivity (68% ee) and conversion (81%) was obtained with ligand **L11** (Scheme 43). **L11** has also demonstrated its ability in the transformation of a series of aryl aldehydes into the (*R*)-desired alcohol in good to high yields (65 to 98%). The enantioselectivities of the alcohol product depend on the electron-donating or electron-withdrawing substituents of the substrate. Thus electron-donating groups show enantioselectivities that are slightly lower (39–64% ee) than that of benzaldehyde (68% ee) but higher than those with electron-withdrawing groups (39–62%).

On the other hand, *para*-substituted aldehydes led to much higher enantioselectivities compared to the *ortho*- or *meta*-aldehydes. Chiral hydroxyalkyl thiazolines (*R*,*S*)-**L12** and (*S*,*S*)-**L12** have shown better performance for this type of transformation. They offer an interesting alternative to carbonyl additions of alkyl- and arylzinc.[84] In the standard $ZnEt_2$ addition towards aromatic aldehydes, the thiazoline ligand (*S*,*S*)-**L12** proved to be efficient, displaying not only a quasi-complete conversion and high enantioselectivity (ee >90%) with aromatic aldehydes, but also relatively good values (70–88% ee) with aliphatic aldehydes (Fig. 3). Note that the mismatched ligand (*R*,*S*)-**L12** gave more or less racemic products in significantly lower yield. (*S*,*S*)-**L12** could be also used to perform the asymmetric addition of phenylzinc with various aromatic and heteroaromatic aldehydes.

The reaction was conducted with the required phenylzinc species obtained *in situ via* the transmetalation of the pinacol ester of phenylboronic acid with diethylzinc in the presence of the hydroxyalkyl thiazoline (*S*,*S*)-**L12** (Scheme 44). This ligand



Scheme 43 Asymmetric addition of Et_2Zn to various aldehydes catalyzed by ligand **L11**.[83]

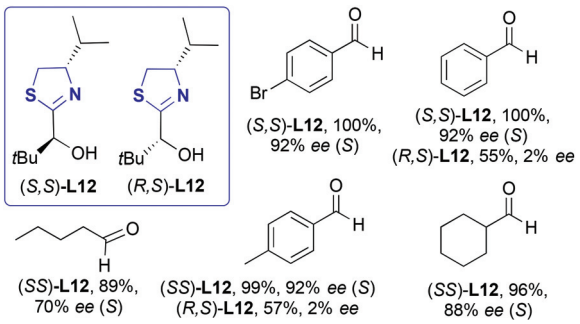
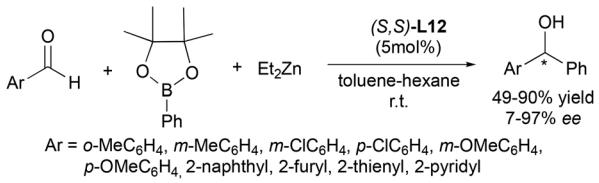


Fig. 3 Et_2Zn addition towards aldehydes catalyzed by ligand **L12**. Reaction performed in toluene/hexane at room temperature for 22 h using 2 mol% of ligands.[84]

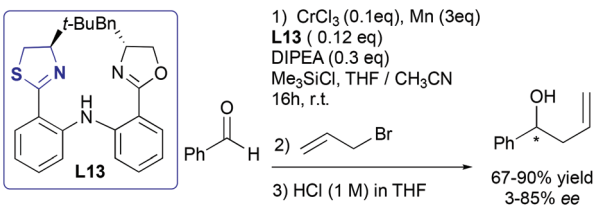


Scheme 44 Phenyl addition towards aldehydes catalyzed by ligand **L12**.[84]

promoted the production of the desired alcohol product in good to high yield (68–90%) except for pyridine carbaldehyde (49%). Excellent ee values were obtained for all aromatic products, relatively independent of the substitution pattern. High ee values (85% ee) were achieved with heteroaromatic aldehydes without nitrogen atoms. The ee values dropped dramatically in the reaction of pyridine carbaldehyde (7% ee) and no reaction was observed with indole carbaldehyde, probably due to the coordination of these N-heterocycles with the zinc reagent.

4.11. Asymmetric Nozaki–Hiyama–Kishi allylation

Guiry *et al.* have also explored the potential of chiral thiazoline–oxazoline ligands in the chromium-catalyzed asymmetric Nozaki–Hiyama–Kishi allylation of benzaldehyde (Scheme 45).[85] The **L13** ligand proved to be an effective catalyst, leading to complete conversion, high yield of the isolated allyl alcohol (84%), and good enantioselectivity (85% ee (*R*)). This ee value is comparable to the ee value of 87% obtained in the allylation of benzaldehyde with the analogue of the *t*-Bu/Bn-substituted bis(oxazoline) ligand.



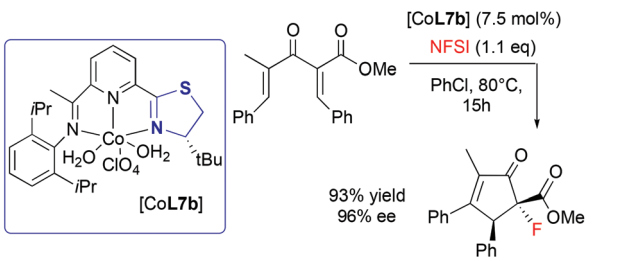
Scheme 45 Chromium catalyzed enantioselective Nozaki–Hiyama–Kishi allylation of benzaldehyde using **L13**.[85]

4.12. Nazarov cyclization/electrophilic fluorination

Lu *et al.* developed the chiral version of the thiazoline iminopyridine, ligand **L7b**, and applied it to the enantioselective cobalt-catalyzed sequential Nazarov cyclization/electrophilic fluorination for obtaining chiral α-fluorocyclopentenones.[86] The Co-complex of the **L7b** ligand proved to be an efficient catalyst in the reaction conducted using α-methyl ester divinyl ketone as the model substrate and NFSI as the fluorinating agent, affording the product in 93% yield with excellent diastereoselectivity (>20/1) and enantioselectivity (96% ee) (Scheme 46). The Co-complex of **L7b** could be used to perform a gram-scale reaction, affording the product in 95% yield with 93% ee. In addition, $[Co(ClO_4)\mathbf{L7b}(H_2O)_2]ClO_4$ was an efficient catalyst under the optimal reaction conditions for the transformation of divinyl ketones with various substituents.

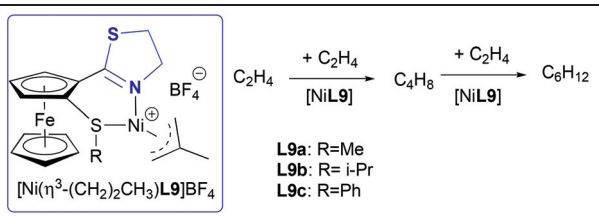
4.13. Ethylene oligomerization

The 2-ferrocenyl thiazolines **L9a–c** were also used in the Ni-catalyzed ethylene oligomerization.[58a,87] Under the optimized conditions, all cationic nickel complexes $[Ni(\eta^3\text{-}(CH_2)_2CMe)\mathbf{L9a–c}]^+$ were efficiently activated for ethylene dimerization, producing butene as a major fraction, with a small number of trimerization products (hexane, up to 11%) (Table 5). The cata-



Scheme 46 [Co**L7b**] catalyzed sequential Nazarov cyclization/electrophilic fluorination of α-methyl ester divinyl.[86]

Table 5 Ethylene oligomerization reactions with complexes $[Ni(\eta^3\text{-}(CH_2)_2CMe)\mathbf{L9}]BF_4$ [a,87]



Entry	Ligand	C4 (%) [selectivity][b]	C6 (%)	TON[c]	TOF (h^{-1})
1	**L9a**	86 [83/11/6]	14	992	3006
2	**L9b**	100 [100/0/0]	—	44	133
3	**L9c**	96 [93/4/3]	4	318	964

[a] The reactions were carried in toluene at 25 °C for 20 min under an ethylene pressure of 12.5 bar in the presence of $B(C_6F_5)_3$. [b] Selectivity = 1-C_4H_8/2-*trans*-C_4H_8/2-*cis*-C_4H_8. [c] TON = mol product per mol Ni.

lytic response of these systems was modulated by the substituents included in the sulfanyl group of the ferrocenyl ligand.

[Ni(η^3-$(CH_2)_2$CMe)**L9a**]BF_4 showed higher activity with a TOF of 3006 h^{-1} and a selectivity of 86% toward the C4 fraction (1-butene/2 butene: 83/17). With ligands **L9b** and **L9c**, the nickel complexes showed a higher selectivity towards the formation of C4 (>96%) but with low activity (TOF = 133 h^{-1} and 964 h^{-1}, respectively).

Braunstein *et al.* also reported on the use of a phosphino-amino-thiazoline ligand **L14** in Ni-catalyzed ethylene oligomerization.[88] The preformed Ni complex exhibits good activities under mild conditions (10 bar, 30 °C) in the presence of $AlEtCl_2$ as the cocatalyst (TOF up to 38 500 h^{-1}) and gave dimers as the major product (73 to 91%). Note that a small percentage of 1-butene was identified (Table 6). Likewise, hexenes and traces of higher olefins were also detected.

4.14. Asymmetric allylic alkylation

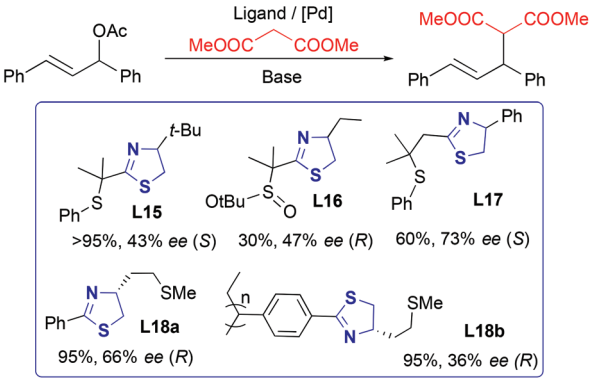
Palladium-catalyzed asymmetric allylic alkylation (AAA) was studied with new families of thiazoline ligands. Previous works have demonstrated the potential of thiazolines in the enantioselective Pd-catalyzed allylic alkylation.[89]

In 2010 Gulea *et al.* described the synthesis of a series of new 2-thiazolines tethered to sulfanyl or sulfinyl groups. Ligands **L15–L18** were evaluated in the palladium-catalyzed AAA.[90] α-Sulfanyl-thiazolines **L15** gave almost complete conversion after 24 h with 43% ee (Scheme 47). α-Sulfinyl-thiazolines **L16** gave a low conversion of 30% after 168 h probably due to the weaker coordination of the metal by the sulfinyl ligand. **L16** gave the (*R*) product in 47% ee, thus the carbon stereocenter in the thiazoline defines the asymmetric induction in the product. With β-sulfanyl-thiazoline ligands, **L17**, conversions were still incomplete after 120 h (50–80%), achieving the best enantiomeric excess (73% ee).

Finally, sulfanyl–thiazoline **L18a** derived from (*S*)-methioninol showed the best performance in terms of conversion and enantioselectivity (total conversion in 24 h and enantiomeric excess of 66%). A polymeric analogue of sulfanylthiazoline, **L18b**, was prepared. When tested under the same conditions, **L18b** showed the same catalytic activity as the corresponding **L18a** ligand.

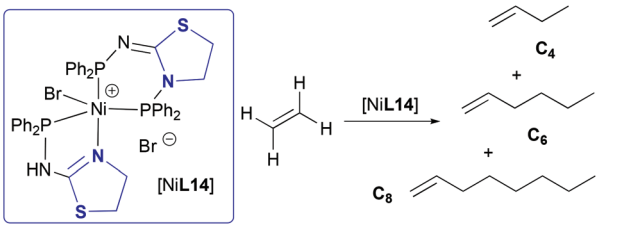
It also favored the formation of the (*R*) product but with a lower enantiomeric excess (36% ee). Attempts to recover and reuse the **L18b**/Pd catalyst led to disappointing results, as conversion and selectivity dropped after the first cycle (15% conversion and 8% ee).

On the other hand, the 2-ferrocenyl-2-thiazoline ligands **L9d–f** appear to be efficient ligands in Pd-asymmetric allylic alkylation. All the ligands performed the reaction at room temperature with quasi-complete conversion and moderate levels of enantioselectivity (60 and 80%).[58b] Lowering the temperature to 10 °C led to incomplete conversion with a notable effect on the enantioselectivity irrespective of the ligands used (Scheme 48). Both activity and enantioselectivity are tunable, modifying the nature of the substituent on the thioether group. With alkyl groups, the conversions are in the range of 71–79% and the enantioselectivity reaches 93–95%, whereas with the phenyl group, both conversion and enantioselectivity decrease dramatically.



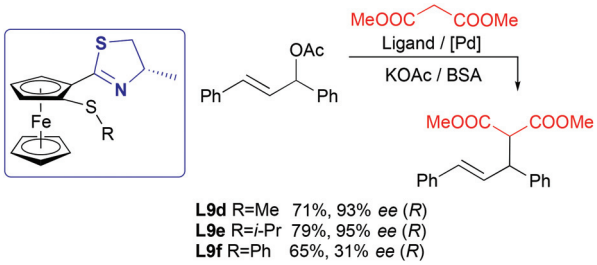
Scheme 47 Pd-Catalyzed asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate using ligands **L15–L18**. The reaction was conducted with 2.5 mol% of $[Pd(allyl)Cl]_2$, 6 mol% of ligand, 0.05 eq. of KOAc, and 3 eq. of BSA in CH_2Cl_2 at RT.[90]

Table 6 Ethylene oligomerization reactions with the nickel complex of **L14** [a,88]

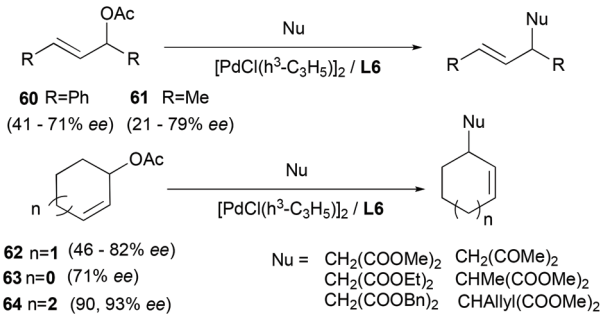


Entry	$AlEtCl_2$ (eq.)	Selectivity (C4/C6/C8)	1-Butene (mol%)	Productivity[b]	TOF[c] (h^{-1})
1	3	91/8/1	17	1386	2900
2	6	85/13/1	14	992	31 700
3	10	73/24/7	6	44	38 500

[a] Reaction conditions: T = 30 °C, 10 bar of C_2H_4, 35 min. [b] Productivity = $gC_2H_4/(gNi)$. [c] TOF = $molC_2H_4/(molNi{\cdot}h^{-1})$.



Scheme 48 Pd-Catalyzed asymmetric allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate using ligands **L9d–f**. The reaction was conducted with 0.5 mol% of $[Pd(allyl)Cl]_2$, 1 mol% of ligand, 0.05 eq. of KOAc, 2 eq. of BSA in CH_2Cl_2 at RT.[58b]



Scheme 49 Different kinds of substrates used in AAA. The reaction was conducted with 0.5 mol% of $[Pd(allyl)Cl]_2$, and 1 mol% of ligand in CH_2Cl_2 at RT.[91,92]

Diéguez *et al.* used the phosphite–thiazoline **L6** ligands for Pd-catalyzed AAS using a broad range of substrates using various carbon nucleophiles (Scheme 49).[91,92] Phosphite–thiazoline ligands **L6** efficiently performed the allylic substitution of symmetrical 1,3-disubstituted allylic substrates with dimethyl malonate as the nucleophile at room temperature under standard conditions (1 mol% of ligand, 0.5 mol% of $[Pd(\eta^3\text{-}C_3H_5)(\mu\text{-}Cl)]_2$, BSA/AcOK as the base, RT, CH_2Cl_2).

The configuration of the alkylation allylic product is governed by the configuration of the alkyl backbone chain. **L6(*R*)** provided lower enantioselectivities (41–71% ee) with the hindered linear substrate **60**, similar enantioselectivities (21–79% ee) with the less sterically hindered linear substrate **61**, and improved enantioselectivities (up to 93% ee) with the more demanding unhindered cyclic substrates (**62**, **63** and **64**). In this case, the best enantioselectivities were obtained with ligand **L6c(*R*)** bearing the trimethylsilyl *ortho*-disubstituted *S*-binol phosphite moiety (93% ee).

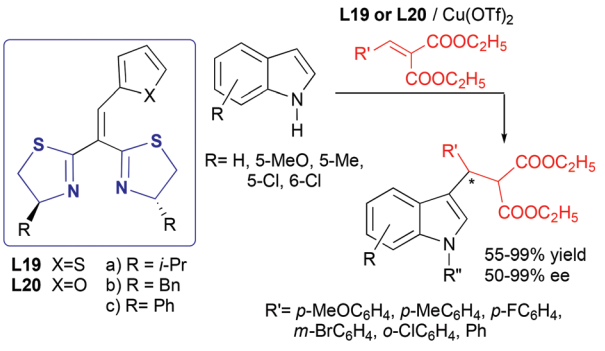
4.15. Asymmetric Friedel–Crafts reaction

Fu *et al.* reported chiral bis(thiazoline) **L19a–c** ligands and evaluated their potential in the asymmetric Cu-catalyzed Friedel–Crafts alkylation of indole with alkylidene malonates (Scheme 50).[93,94] In the alkylation of indole with diethyl benzylidene malonate, the **L19a–c**/$Cu(OTf)_2$ system gave full conversion within 24 h in different alcoholic solvents at room temperature. The enantiomeric excess of the indole adduct was significantly affected by both the substituents on the thiazoline ring and the heterocycle moiety attached to the double bond. Ligands **L19a–c** with a thienyl group gave very poor enantioselectivities (9–16% ee). In contrast, **L20a–c** containing a furyl group showed good to high enantioselectivities (52–99% ee), with **L20b** showing the best performance (99% yield and >99% ee).

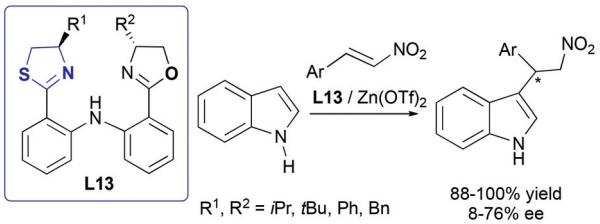
Thus, the **L20b**/$Cu(OTf)_2$ system proved to be an efficient catalytic system for the alkylation of various indole derivatives with different arylidene malonates. Both activity and selectivity depend on the substituents on the indole and/or arylidene malonates. Excellent results were achieved for the reaction of indole with three arylidene malonate substrates with 4-MePh, 4-MeOPh, and 4-FPh groups (99% yield and 98–99.5% ee). The authors suggest that the bis(thiazoline) **L19** and **L20** ligands behave as [N,N] ligands towards the metal center. The furan or thiophene moiety can participate in weakly intermolecular coordination *via* a second ligand molecule. The best enantioselectivities offered by the ligands **L20b** and **c** are attributed to the furan fragment which is more effective in a chiral environment than thiophene.

In this context, the group of Guiry synthesized a family of chiral tridentate [*N*,*N*,*N*]-thiazoline-oxazoline ligands **L13** which were applied in the Zn-catalyzed asymmetric Friedel–Crafts alkylation of indole with various electron-deficient alkenes (Scheme 51).[85,95] All **L13** ligands promoted the quasi-complete Friedel-Crafts reaction of indole with *trans*-β-nitrostyrene (94 to 100% yield) in toluene at −20 °C using 5 mol% of the $Zn(OTf)_2$/ligand **L13** as the catalytic system. Poor enantioselectivities (8–19% ee) were obtained using both R^1, and R^2 alkyl substituents. Enantiomeric excess values were greatly improved (51–71% ee) with the use of ligands with phenyl or benzyl groups. A better enantiomeric excess value was obtained when the aromatic group on the oxazoline ring and the alkyl substituent on the thiazoline ring were included.

In addition, this ligand was applied in the asymmetric Friedel-Crafts reaction of indole with β-nitrostyrene substrates possessing a range of steric and electronic variations. **L13** provided efficient catalysts that show quasi-complete conversion of all substrates (88–100% yield) but with variable levels of enantioselectivity (17–76%).



Scheme 50 The **L19** or **L20**/$Cu(OTf)_2$ system catalyzed Friedel–Crafts reaction of indole with alkylidene malonates. Reactions were conducted in ethanol under nitrogen using 10 mol% catalyst at room temperature.[93]



Scheme 51 **L13**/$Zn(OTf)_2$ catalyzed Friedel–Crafts reaction of indole with *trans*-β-nitrostyrene derivatives. Reactions were conducted in toluene at −20 °C for 15 h using 5 mol% catalyst.[95]

5. Conclusions

In the last twelve years, the use of amino thiols and amino alcohols continues to be an option for the synthesis of 2-thiazolines. However, catalytic approaches employing nitriles and aminothiols have emerged as good alternatives for accessing these types of heterocycles.

On the other hand, the methods with amino alcohols have shown an improvement in the use of new dehydrating agents in the ringing of β-hydroxy thioamides.

Likewise, the use of different thioamides not derived from amino alcohols has set a new guideline in obtaining these heterocycles, allowing the synthesis of 4- or 5-functionalized thiazolines. Advantages such as avoiding the use of thionating reagents, long synthesis routes, or drastic reaction conditions show the importance of these new approaches. Although most of these methods provide new 2-phenyl, pyridyl, thionyl, ferrocenyl, amino, and alkyl thiazolines, the challenge of expanding these methodologies to 2-alkyl thiazolines whose yields are still low remains.

Concerning their reactivity, 2-thiazolines have shown remarkable development in the synthesis of 4,4-disubstituted thiazolines, which are the raw materials of α-alkyl cysteines.

Likewise, thiazolines as ligands in catalysis continue to attract the interest of the synthetic community. Thus, an increase in their use and studies on new catalytic applications has been observed in the last few years. Reactions such as styrene isomerization, C–C coupling, sulfide oxidation, amine alkylation, ethylene oligomerization, allylic oxidation, arylation using zinc reagents, hydrogenation, Nazarov cyclization, and Nozaki–Hiyama–Kishi allylation are examples where 2-thiazolines have been used recently.

There is still a lot to know about the potential applications of 2-thiazolines, expanding their use in molecular catalysis or designing new or novel immobilizing strategies that are focussed on facilitating their reuse and recyclability as a strategy to improve their catalytic performance.

Conflicts of interest

There are no conflicts to declare.

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