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(*N*,*N*) vs. (*N*,*S*) chelation of palladium in asymmetric allylic substitution using bis(thiazoline) ligands: A theoretical and experimental study

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ABSTRACT

New thiazoline-containing ligands including non-symmetric bis(thiazolines) and oxazoline–thiazolines were synthesized and then compared to C_2-symmetric bis(thiazolines) in the palladium-catalyzed allylic substitution. The experimental results obtained in this study support the hypothesis of a competition between the (*N*,*N*) and the (*N*,*S*) palladium chelation, when sterically hindered bis(thiazolines) are used as ligands. A quantum chemical study performed on the Pd-complexes derived from three selected ligands, two C_2-symmetric bis(thiazolines) and one oxazoline–thiazoline, also supports this hypothesis.

1. Introduction

Compared to the widely applied oxazoline ligands in asymmetric catalysis [1], their sulfur analogues, the thiazolines, have been rarely used for this purpose. The first study dealing with chiral thiazoline ligands was reported by Helmchen in 1991 and found a different behaviour compared to oxazolines in the rhodium catalyzed asymmetric hydrosilylation of acetophenone [2]. In fact, the real interest in thiazoline ligands only appeared ten years later. Since then, their structures and applications have been regularly renewed [3,4]. In some studies, thiazoline ligands have been evaluated and compared to the corresponding oxazolines in well known metal-catalyzed asymmetric reactions [2,3b,3c,4]. As expected, different results have been noticed for the two types of ligands, due to electronic and steric effects resulting from the substitution of the oxygen atom by a sulfur in the heterocycle [5]. Thus, further investigations appear necessary for a favourable development of thiazoline ligands, shedding light on the behaviour of the thiazoline heterocycle towards the metal chelation.

In a previous paper [3b], some of us reported the synthesis of various thiazolines, analogous to the well known oxazoline ligands, and their evaluation in the enantioselective Pd-catalyzed allylic substitution [6], one of the benchmark reactions in asymmetric catalysis to test the efficiency of new ligands. The results were compared with those obtained with the oxazoline counterparts and important differences in the behaviour of the two types of ligands were found in some cases. Moreover, unexpected results were obtained in the bis(thiazoline) series (Scheme 1): (i) the enantiomeric excess decreases with the increase of the steric hindrance of the substituent in 4-position of the heterocycle [ee: 88% (Et) > 42% (*i*Pr) > 31% (*t*Bu)]; (ii) while bis(thiazolines) (*R*,*R*)-**1a** and (*R*,*R*)-**1b** led to the major enantiomer (*R*) of the product, bis(thiazoline) (*S*,*S*)-**1c**, which was expected to give major (*S*)-enantiomer, led to the opposite enantiomer (*R*).

To explain these results, a competition between nitrogen and sulfur in the palladium chelation was proposed in our previous paper [3b] (Scheme 2). For the (*R*,*R*)-bis(thiazoline) **1a**, the reaction should proceed as for a C_2-symmetric bis(oxazoline) [7], involving a complex in which Pd is chelated by two nitrogen atoms. The nucleophilic attack takes place on the allylic carbon with the longest Pd–C distance, leading to a major (*R*) product. An important increase of the steric hindrance of the substituent (R = *t*Bu), could cause the rotation of one of the thiazoline cycles to release the constraint, leading to a (*N*,*S*)-chelation of the palladium by a bis(thiazoline). Therefore, the C_2-symmetric bis(thiazoline) would become a C_1-symmetric sulfanyl–thiazoline ligand, which would lead to two diastereomeric Pd-complexes in equilibrium. These diastereomers would lead, according to a nucleophilic attack on the allylic carbon *trans* to the sulfur atom, to opposite enantiomers of the product [8,9]. The possible formation and co-existence of three palladium

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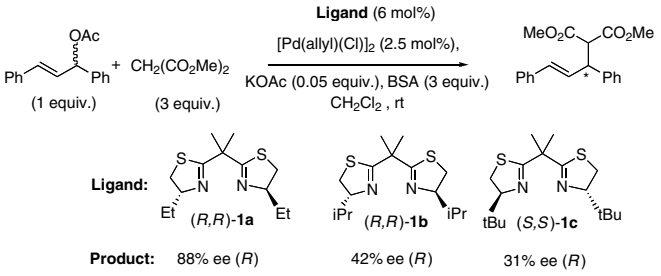
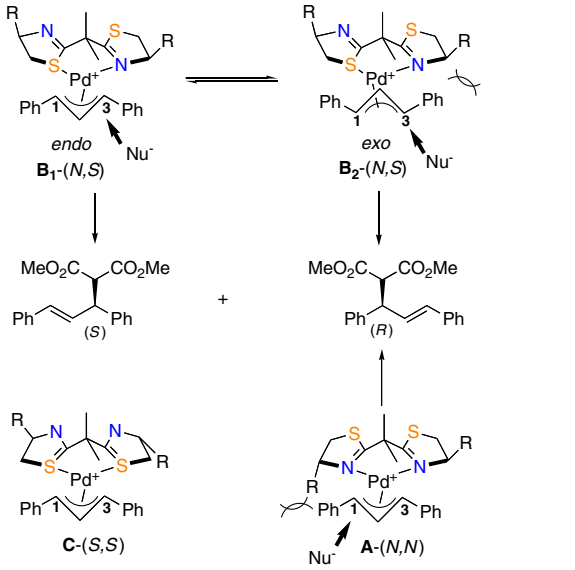


Scheme 1. Pd-catalyzed allylic substitution using bis(thiazolines) **1**.



Scheme 2. Proposed palladium complexes in the reaction mixture involving bis(thiazolines) **1**: complex **A**-(*N*,*N*), two diastereomeric complexes $\mathbf{B}_1$-(*N*,*S*)-*endo* and $\mathbf{B}_2$-(*N*,*S*)-*exo*, and *C*-(*S*,*S*).

complexes as intermediates in the reaction mixture (see complexes **A**, $\mathbf{B}_1$, and $\mathbf{B}_2$ in Scheme 2), each one leading preferentially to one enantiomer of the product, could explain the decrease of the enantiomeric excess, as well as the inversion of the enantioselection, depending on the steric hindrance of the R substituent. It is worth noting that the possibility of a *S*,*S*-chelation of the metal (complex *C*) cannot be excluded. In that case the chirality would certainly be placed too far from the chelation site to induce enantioselectivity, however, the consequence could be the decrease of the enantiomeric excess.

To support this hypothesis we undertook a new study. First, to determine the catalytic effect induced by different modifications around the metal site, we synthesized new thiazoline ligands (Fig. 1): non-symmetric bis(thiazolines), in which the two heterocycles bear substituents ($R^1 \neq R^2$) of different steric hindrance [10], and oxazoline–thiazolines, in which only one of the heterocycles, the thiazoline, can coordinate the Pd by either the nitrogen or the sulfur atom. Then, these ligands were tested in the Pd-catalyzed allylic substitution. The second part of the study consisted in a theoretical approach. Simplified structures of an oxazoline and of a thiazoline were first compared in terms of geometric and electronic properties, which can explain their different complexing behaviours toward a metal. Then, a quantum chemical study of three π-allylic palladium complexes was carried out involving as representative ligands the two C_2-symmetric bis(thiazolines) **1a** (R = Et) and **1c** (R = *t*Bu) and the oxazoline–thiazoline **4a**. The experimental and theoretical results of the study are discussed in this paper.

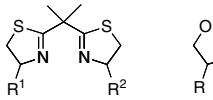


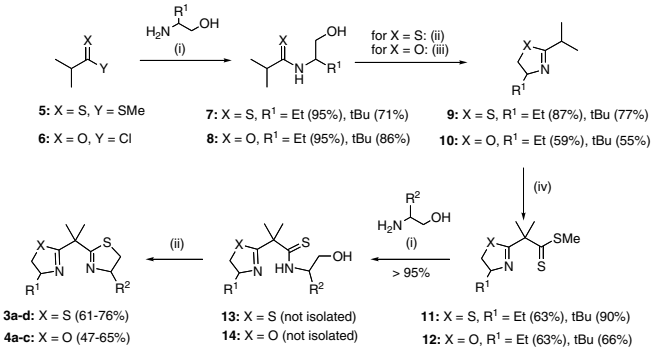
Fig. 1. Non-symmetric bis(thiazolines) and oxazoline–thiazoline ligands.

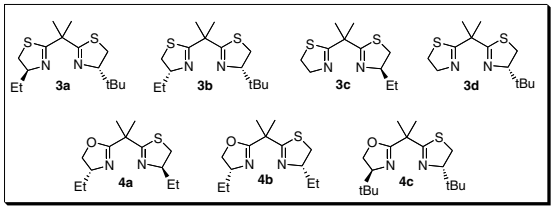
2. Results and discussion

2.1. Synthesis of non-symmetric bis(thiazolines) and oxazoline–thiazoline ligands

Four non-symmetric bis(thiazolines) **3a**–**3d** and three oxazoline–thiazolines **4a**–**c** were designed as target structures for this study (see Scheme 3, Table 1). Derivatives **3a** and **3b** have different substituents on the thiazoline heterocycles (Et and *t*Bu): **3a** has the same configuration (*S*) on the two heterocycles, whereas **3b** has (*R*) configuration on the ethyl substituted thiazoline, and (*S*) on the *tert*-butyl substituted cycle. Bis(thiazolines) **3c** and **3d** have one non-substituted thiazoline cycle, and the other cycle substituted by an ethyl group having (*R*) configuration for **3c**, and by a *tert*-butyl having (*S*) configuration for **3d**. Mixed oxazoline–thiazoline ligands **4a** and **4b** are substituted by the same substituent (ethyl) on each heterocycle, but **4a** has (*R*,*R*)-configuration, while **4b** has (*R*) configuration on the oxazoline and (*S*) on the thiazoline ring. Oxazoline–thiazoline **4c** has substituent on both heterocycles and (*S*,*S*)-configuration.

The general synthesis of bis(thiazolines) **1** from commercially available aminoalcohols that we developed previously [3a], has the advantage of a stepwise construction of the two thiazoline rings, allowing the introduction of two different 2-aminoalcohols in the same chiral backbone, and, therefore, the synthesis of non-symmetric bis(thiazolines) such as **3** (Scheme 3). In the first step, thioamides **7** were prepared by thioacylation of the commercially available aminoalcohols [(*R*)- and (*S*)-2-aminobutanol, (*S*)-*tert*-leu-





Scheme 3. Synthesis of non-symmetric bis(thiazolines) **3**, and oxazoline–thiazolines **4**.

Table 1
Synthesis of thiazoline ligands **3a**–**3d** and **4a**–**4c**

Ligand	R^1	R^2	Config	Overall yield (%)
3a	Et	*t*Bu	(S_{Et},S_{tBu})	35 [a]
3b	Et	*t*Bu	(R_{Et},S_{tBu})	34 [a]
3c	H	Et	(*R*)	40 [a]
3d	H	*t*Bu	(*S*)	30 [a]
4a	Et	Et	(R_{oxa},R_{thia})	17 [b]
4b	Et	Et	(R_{oxa},S_{thia})	23 [b]
4c	*t*Bu	*t*Bu	(S_{oxa},S_{thia})	20 [b]

[a] From dithioester **5**.
[b] From 2-methyl-propanoyl chloride **6**.

cinol] with dithioester **5**. The non-substituted thiazoline ring (R^1 or R^2 = H) obtained from the appropriate dithioester (**5** or **11**) and 2-bromoethanolamine hydrobromide, by a one-step thioacylation/cyclisation [11]. The intramolecular cyclisation of **7** via a mesylate led to monothiazolines **9**, which were deprotonated by *t*-BuLi to introduce a new dithioester function, by reaction with carbon disulfide and trapping of the anion with methyl iodide. From the resulting thiazoline-dithioester **11** the same subsequent two-step process thioacylation/cyclisation led to non-symmetric bis(thiazolines) **3**. Based on **5**, the overall yields are given in Table 1. The same methodology was used to prepare oxazoline–thiazolines **4** (Scheme 3). The sequence started in this case with the synthesis of the oxazoline heterocycle. Oxazolines **10** were obtained in two steps starting from 2-methyl-propanoyl chloride **6** and enantiopure 2-aminoalcohols [12]. Mitsunobu conditions [13] were used for the cyclisation of β-hydroxy amide **8** to the corresponding oxazoline. After introduction of the dithioester group and formation of the thiazoline ring, oxazoline–thiazolines **4** were obtained, in overall yields based on **6**, which are given in Table 1.

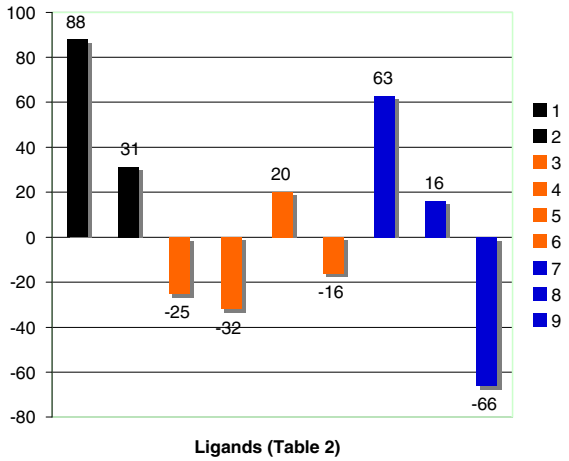
2.2. Pd-catalyzed allylic substitution using thiazoline-containing ligands

The newly synthesized ligands **3** and **4** were tested in the Pd-catalyzed allylic substitution in the conditions used before for bis(thiazolines) **1a** and **1c** (see conditions in Scheme 1). The reaction which used 1,3-diphenyl-2-propenyl acetate and dimethylmalonate, in the presence of 2 equiv. of bis(trimethylsilyl)-acetamide (BSA) and 5 mol% of potassium acetate (AcOK) [14], was carried out in dichloromethane, at room temperature, using 2.5 mol% of $[Pd(C_3H_5)Cl]_2$, 6 mol% of ligand, and afforded (*E*)-2-methoxycarbonyl-3,5-diphenylpent-4-enoate as product. The results are given in Table 2 and the enantiomeric excesses are also represented in Graph 1 to facilitate comparison. In all cases the conversion was almost complete (>95%) after about 24 h, except for ligand **4c** [15]. Although a rationalization of the obtained results by considering all the possible transition states in the reaction would be very complex, a qualitative analysis is accessible and should help to understand the origin of the asymmetric induction.

Table 2
Pd-catalyzed asymmetric allylic substitution using thiazoline ligands **1a**, **1c**, **3a**–**3d**, and **4a**–**4c**

Entry	Ligand[a]	Conv. (%)[b] (Time)	Ee%[c]	Product configuration[b]
1	**1a**	>95 (24 h)	88	(*R*)
2	**1c**	>90 (30 h)	31	(*R*)
3	**3a**	100 (24 h)	25	(*S*)
4	**3b**	100 (24 h)	32	(*S*)
5	**3c**	100 (24 h)	20	(*R*)
6	**3d**	100 (24 h)	16	(*S*)
7	**4a**	100 (24 h)	63	(*R*)
8	**4b**	>95 (24 h)	16	(*R*)
9	**4c**	25 (168 h)	66	(*S*)

[a] For comparison, data for ligands **1a** and **1c** already published [3b] are included.
[b] Determined by HPLC.
[c] Each experiment was carried out at least two times.



Graph 1. Comparative graph: Ee (%) with bis(thiazolines) of C_2-symmetry **1a** and **1c** (1–2) and of C_1-symmetry **3a**–**3d** (3–6), and with oxazoline–thiazolines **4a**–**4c** (7–9). Ees (%) are given in positive values for the (*R*) enantiomer and in negative ones for the (*S*) enantiomer.

Results obtained with non-symmetric bis(thiazolines) **3a** and **3b** show that the sense of the induction is determined by the bulkier substituent. Thus, ligands **3a** and **3b**, which are diastereomers having on the thiazoline bearing the *tert*-butyl substituent the same configuration, and on the thiazoline bearing the ethyl substituent opposite configurations, gave quite similar enantiomeric excess (25% and 32%, respectively) in favour of the (*S*) product (Table 2, entries 3 and 4). This suggests that the configuration on the thiazoline bearing the smaller ethyl group did not determine the asymmetric induction. However, it is worth noting that the decrease of the steric hindrance on one of the thiazolines restores the "normal" sense of the induction (Table 2, entries 2 and 3). Thus, (*S*) thiazoline ligand bearing a *tert*-butyl group afforded (*S*)-enantiomer as the major enantiomer. This can be considered as an experimental evidence to support the hypothesis that the unexpected sense of the induction obtained in the case of ligand **1c** is due to the release of the steric strain by rotation of the thiazoline cycle and coordination of the sulfur atom to the palladium, through a (*N*,*S*) chelation. Equally, changing from **1c** to **3d** (suppression of one *tert*-butyl substituent) the sense of the induction was reversed from (*R*) to (*S*) (Table 2, entries 2 and 6). Going from **1a** to **3c** (suppression of one ethyl substituent) the sense of the enantioselectivity was kept affording the same major (*R*) product, but with a strong decrease of the enantiomeric excess from 88% to 20%, due very probably to the loss of the C_2-symmetry, but also to the low steric hindrance of this ligand (Table 2, entries 1 and 5). This first set of results shows the great influence of steric parameters on the stereoselectivity of this reaction.

Then, the oxazoline–thiazolines series was examined. First, ligand **4a** was compared to bis(thiazoline) **1a**, both having (*R*,*R*) configuration and ethyl substituents on both heterocycles (Table 2, entries 1 and 7). (*R*)-enantiomer was obtained as the major enantiomer in both cases, but the enantiomeric excess decreased from **1a** (88%) to **4a** (63%). Oxazoline–thiazoline **4b**, which is the diastereomer of **4a** having the same configuration on the oxazoline ring and opposite configuration on the thiazoline one, gave (*R*)-product in only 16% ee (Table 2, entry 8). Finally, ligand **4c** was compared to bis(thiazoline) **1c**, both having (*S*,*S*) configuration and *tert*-butyl substituents on both heterocycles (Table 2, entries 2 and 9). From **1c** to **4c**, the sense of the enantioselectivity was reversed and the enantiomeric excess increased from 31% to 66% [16]. In the case

of an oxazoline–thiazoline, both supposed (*N*,*N*) and (*N*,*S*) Pd-complexes should have two diastereomers, $\mathbf{A}_1/\mathbf{A}_2$ and $\mathbf{B}_1/\mathbf{B}_2$, respectively. The four complexes from a (*R*,*R*) oxazoline–thiazoline ligand of type **4a** are represented in Scheme 4. For both complexes $\mathbf{A}_1$ and $\mathbf{A}_2$, the steric hindrance between the R substituent and the phenyl group of the allylic part should direct the sense of the asymmetric induction toward the (*R*)-product. The *N*,*S*-complexes $\mathbf{B}_1$ and $\mathbf{B}_2$ should lead to (*S*) and (*R*) enantiomer respectively, according to the nucleophilic attack in *trans* position to the sulfur atom. In the case of $\mathbf{B}_1$, the carbon atom *trans* to the sulfur is also the most sterically congested. In the case of (*R*)-oxazoline-(*S*)-thiazoline **4b**, the low ee obtained (16%) can be explained by the lack of a good enantiodiscrimination between the two allylic carbons in the considered diastereomeric *N*,*N*-complexes $\mathbf{A}_1/\mathbf{A}_2$ (Scheme 5).

2.3. Oxazoline/thiazoline comparison

The unlike behaviour of thiazoline and oxazoline ligands could result from several factors such as the heterocycle geometry, and the modified features of the electronic structure of both ligands (as deduced, e.g., by inspection of the change of the frontier orbitals). Thiazoline **I** and oxazoline **II** have been used as simple models for theoretical calculations (Fig. 2). Their geometries were optimized, and bond lengths, angles, and electronic densities were calculated for both heterocycles (Table 3). Due to the difference between the carbon-heteroatom bond lengths and angles, the two heterocycles have different geometries. Compared to the quasi-planar geometry of oxazolines, thiazolines have a distorted and larger ring. This may cause, especially when the heterocycles are substituted, steric interactions in the metal–ligand complex, which can influence the enantioselectivity. Moreover, the important difference of electronegativity between oxygen and sulfur can explain the different electronic repartition in the two heterocycles.

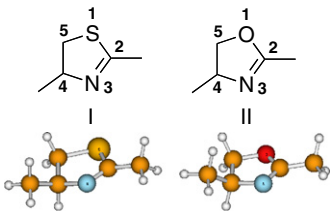


Fig. 2.

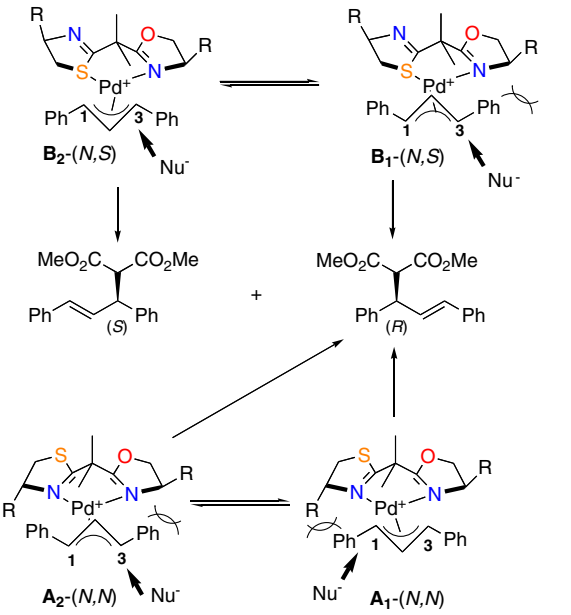
Table 3
Optimized bond lengths in Å, bond angles in degrees and selected atomic charges (q) obtained with the natural population analysis (BP86/TZVP) for structures **I** and **II**

Heterocycle	Thiazoline **I**	Oxazoline **II**
Length (Å) C–X[a]	1.821	1.381
Length (Å) C=N	1.275	1.279
Angle (°) C^2–X–C^5	89.12	105.02
Angle (°) X–C^2–N	117.43	118.54
Dihedral angle X–C^5–C^4-N	26.06	11.30
$q_{(N)}$	−0.392	−0.437
$q_{(X)}$	+0.162	−0.445

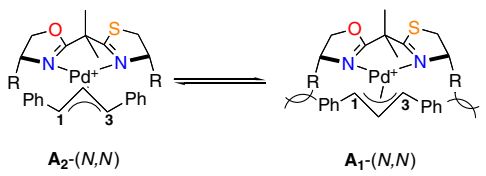
[a] The sulfur and oxygen atoms in **I** and **II**, respectively, are denoted by an "X" in the 1st column.

As shown in Table 3, according to the results obtained from natural population analysis, the negative atomic charge of nitrogen in oxazoline **II** is slightly higher than it is in thiazoline **I**, and the atomic charge is positive for sulfur and negative for oxygen. This is in accord with the fact that sulfur's electronegativity is similar to the one of carbon and lower than oxygen and nitrogen electronegativities [C (2.5) = S (2.5) < N (3.0) < O (3.5)] [17].

For a qualitative picture of the complexation of the metal with an oxazoline or a thiazoline ligand, the HOMO should also be considered. As shown in Fig. 3, for oxazoline **II**, the largest part of the HOMO is located on the nitrogen atom, however, the oxygen atom contributes also significantly. In contrast, the HOMO of thiazoline **I** is located on the sulfur atom (which may be taken as an indication for its affinity to soft metals), while the contributions on the nitrogen atom are relatively small. This may be seen as an indication of differences in the type of chelation and in the stability of the complexes (qualitatively speaking, the HOMOs of these sigma-donor ligands will govern the donation of electron density to the transition metal atom).



Scheme 4. Proposed palladium complexes involving a (*R*)-oxazoline-(*R*)-thiazoline in the reaction mixture: two *N*,*N*-complexes $\mathbf{A}_1$ and $\mathbf{A}_2$ and two *N*,*S*-complexes $\mathbf{B}_1$ and $\mathbf{B}_2$.



Scheme 5. (*N*,*N*) complexes **A1** and **A2** involving a (*R*)-oxazoline-(*S*)-thiazoline ligand.

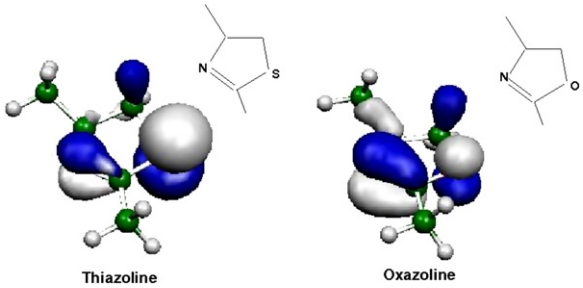


Fig. 3. HOMO of thiazoline **I** and of oxazoline **II** (both have been plotted with the same isosurface value).

These data show important differences between a oxazoline and its thiazoline analogue and let us anticipate a different behaviour in the metal coordination (and therefore their different catalytic activities and enantioselectivities).

2.4. Quantum chemical study of the π-allylic palladium complexes involving bis(thiazolines) **1a**, **1c**, and **4a**

The reaction mechanism and the possible modes of stereoselection in palladium-catalyzed allylation are well studied [6]. With symmetrically substituted allyl moiety (such as in the 1,3-diphenyl-2-propenyl acetate), the stereoselection results from the difference in reactivity of the allyl termini in the nucleophilic addition step. It was shown that in a *meso*-(π-allyl)palladium complex, the carbon with the longest distance to Pd is preferentially attacked by the nucleophile [6]. The Pd–C bond elongation can come from a steric congestion, or, like in the case of C_1-symmetric ligands with different donor heteroatoms, from the strong donating effect of one atom (provoking the bond elongation *trans* to this atom). Some theoretical studies have been done to gain a better understanding of the enantioselectivity of this reaction [18]. According to one model, an elongation of the Pd–C bond by $\Delta l = 0.01$ Å will approximately double the reactivity at this carbon [18h]. It was also established that in the case of a C_1-symmetric ligand, the equilibrium between the two diastereomeric complexes [6] occurs faster than the nucleophilic attack. Therefore, interpretation of the theoretical results should be considered carefully, since the rate-limiting and selectivity-determining steps do not have to be the same.

For the theoretical investigation performed in this work we assume that all diastereomers can interconvert. Thus, barriers are expected to be small, an equilibrium is established and the reaction products are therefore determined by the relative thermodynamic stability of the different structures. Consequently, we deem it sufficient to analyse the stable minimum structures of all relevant diastereomers. In order to do so, we only consider the difference in electronic energy at 0 K. This is sufficient because temperature effects on the enthalpy and on the entropy as well as the zero-point vibrational energy can safely be neglected because of the high similarity of all structures under consideration. The electronic energy differences allow us to discuss purely electronic effects.

As a first step, we carried out a theoretical investigation of palladium complexes involving bis(thiazolines) **1a** and **1c**. In Figs. 4–6 the optimized geometries (BP86/RI/TZVP) are shown and the corresponding relative energies of the intermediate complexes with ligands **1a** (Fig. 4), **1c** (Fig. 5), and **4a** (Fig. 6) are given. For comparison, single-point energies from B3LYP/TZVP//BP86/RI/TZVP calculations are given in parentheses. In addition, selected carbon–palladium (Pd–C^1 and Pd–C^2) bond distances are given in angstroms. The *S,S*-complex *C* was taken into consideration only

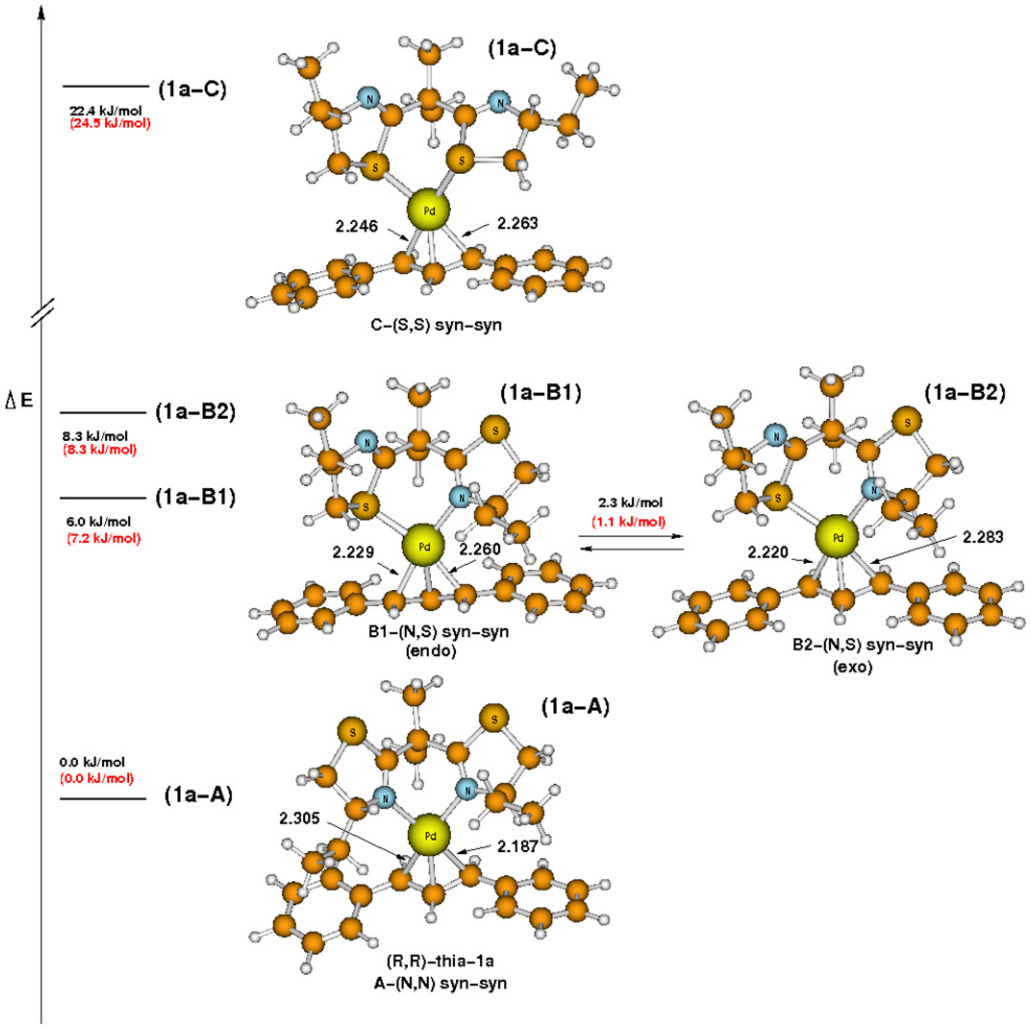


Fig. 4. BP86/RI/TZVP-optimized structures and energies of Pd-complexes with ligand **1a**.

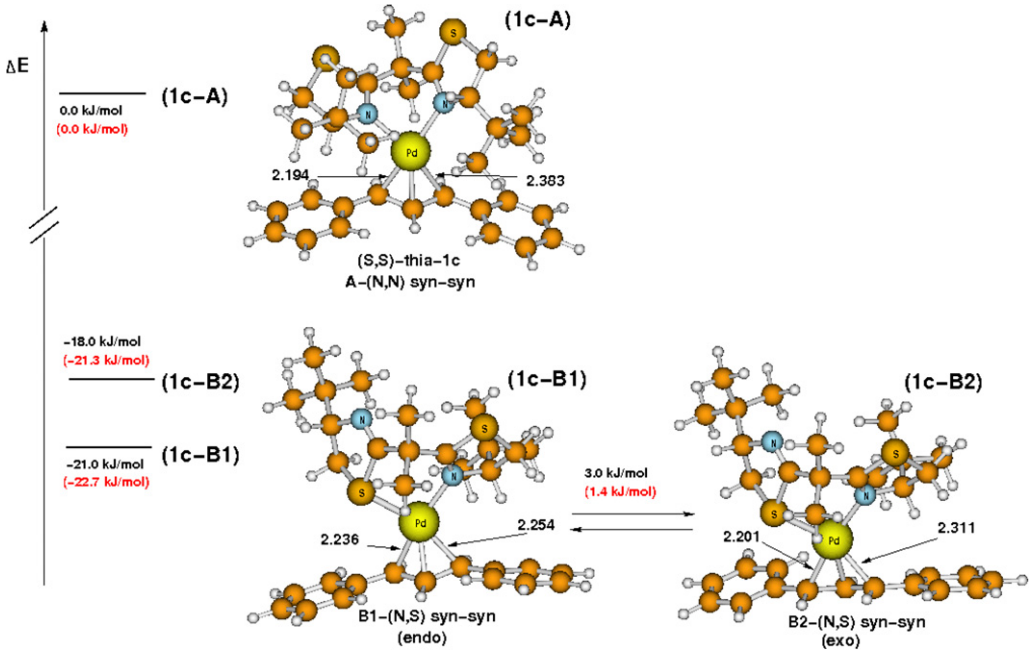


Fig. 5. BP86/RI/TZVP-optimized structures and energies of Pd-complexes with ligand **1c**.

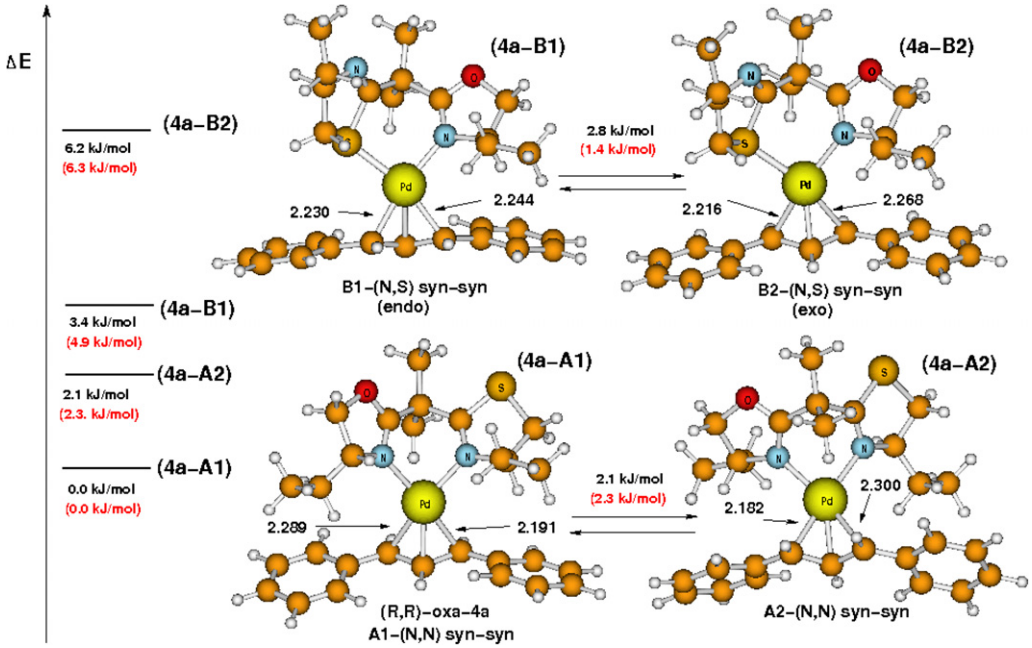


Fig. 6. BP86/RI/TZVP-optimized structures and energies of Pd-complexes with ligand **4a**.

in one example (for ligand **1a**), since steric or electronic factors could not influence the enantioselectivity in this case, and they probably not vary from one ligand to another. However, to compare its stability with those of the *N*,*N* and *N*,*S* complexes could give an indication of its responsibility for a low ee.

Fig. 4 shows that the stability of the complexes decreases in the order **1a-A** > **1a-B**$_1$ > **1a-B**$_2$ > **1a-C**. The *N*,*N*-complex **1a-A** is 6.0 and 8.3 kJ/mol more stable than the two *N*,*S*-complexes **1a-B**$_1$/**B**$_2$, respectively. Complex **1a-C** was found to be the least stable (22.4 kJ/mol less stable than **1a-A**), therefore, its contribution in the context of this study can be neglected. Complex **1a-B**$_2$ was calculated to be less stable than its diastereomer **1a-B**$_1$, however, the difference of energy is small (2.3 kJ/mol) and hence almost negligible. According to the calculated Pd–allylic carbon bond lengths (see Table 4), complexes **1a-A** and **1a-B**$_1$ may lead to the main product having (*R*) configuration, while **1a-B**$_2$ may lead to the opposite enantiomer (*S*), since nucleophilic attack occurs on the carbon with the longest Pd–C bond. These theoretical data suggest that the nucleophile attacks preferentially the carbon C^1 of the *N*,*N*-complex **1a-A**, leading to (*R*) enantiomer as the major product. These theoretical results are thus in agreement with the experimental results obtained in the case of bis(thiazoline) ligand **1a** (88% ee in favour of the *R* enantiomer). Fig. 5 shows that the stability of the complexes decreases in the order **1c-B**$_1$ > **1c-B**$_2$ > **1c-A**. It could

Table 4
Calculated elongation $\Delta l = |(Pd–C^1)–(Pd–C^3)|$ and expected configuration of the product, for allyl palladium complexes derived from ligands **1a**, **1c**, and **4a**

Ligand	**1a**				**1c**			**4a**			
Complex	**1a-A**	**1a-B1**	**1a-B2**	**1a-C**	**1c-A**	**1c-B1**	**1c-B2**	**4a-A1**	**4a-A2**	**4a-B1**	**4a-B2**
Δl (Å)	0.118[a]	0.031	0.063	0.017	0.189[a]	0.018	0.110	0.098	0.118[a]	0.014	0.052
Predicted configuration[b]	(*R*)	(*R*)	(*S*)	(*S*)	(*S*)	(*S*)	(*R*)	(*R*)	(*R*)	(*R*)	(*S*)

[a] Most important elongation for each case of ligand.
[b] The predicted configuration of the product is that resulting from the nucleophilic attack on the Pd-complexes **A**, **B**, or *C* corresponding to ligands **1a** and **1c** (see Scheme 2) and to ligand **4a** (see Scheme 4).

be immediately noticed that in contrast with the previous case of **1a** (with Et substituents), in the case of ligand **1c** (with bulky *t*Bu substituents) the *N*,*N*-complex **1c-A** is the least stable. Moreover, the difference of energies between complexes **1c-B**$_2$/**B**$_1$ and **1c-A** becomes more important (18 and 21 kJ/mol, respectively). The diastereomeric complexes **1c-B**$_2$ and **1c-B**$_1$, which are very close in energy (3 kJ/mol in favour of **1c-B**$_1$), would lead to products with opposite configuration. Therefore the low ee observed is not surprising.

For the palladium complexes involving the mixed thiazoline–oxazoline ligand **4a** (Fig. 6) four complexes are considered, and their stability decreases as follows: **4a-A**$_1$ > **4a-A**$_2$ > **4a-B**$_1$ > **4a-B**$_2$ (ΔE = 6.2 kJ/mol between the most stable and the less stable complex). As with bis(thiazolines) **1a** and **1c**, the calculated energy difference between the two diastereomeric complexes **4a-B**$_1$ and **4a-B**$_2$ is negligible (2.8 kJ/mol). The calculated energy difference between the diastereomeric complexes **4a-A**$_1$ and **4a-A**$_2$ is also small (2.1 kJ/mol). According to the nucleophilic attack on the carbon with the longest Pd–C bond, complexes **A**$_1$, **A**$_2$ and **B**$_1$ may lead to the main product of (*R*) configuration, while complex **B**$_2$ may lead to the opposite enantiomer (*S*). These theoretical data can again be correlated to the experimental result obtained with **4a** (63% ee and *R* configuration of the product).

In Table 4 are given for each complex derived from ligands **1a**, **1c**, and **4a**, the calculated elongation Δl of one palladium–carbon bond in the 1,3-diphenylallyl palladium complexes and the expected configuration of the product. In the three studied cases, an elongation between 0.01 and 0.19 Å was found. For all *N*,*S*-complexes (**B**), the longest Pd–C distance was found to be *trans* to the sulfur atom. These theoretical results are in agreement with the expected influence of the steric hindrance of the substituents and with the strong *trans* effect of sulfur in this type of ligands.

3. Conclusion

New thiazoline-containing ligands including non-symmetric bis(thiazolines) and oxazoline–thiazolines were synthesized and then compared to C_2-symmetric bis(thiazolines) in the palladium-catalyzed allylic substitution. The experimental results obtained in this study support the hypothesis of a competition between the (*N*,*N*) and the (*N*,*S*) palladium chelation when bis(thiazolines) are used as ligands, and reveal the importance in this reaction of the steric hindrance of the R substituent in alpha position to the nitrogen atom. A quantum chemical study on the Pd-complexes derived from three selected ligands, two C_2-symmetric bis(thiazolines) (substituted by R = Et and *t*Bu, respectively) and one oxazoline–thiazoline, was also performed. Although the obtained theoretical results should be considered carefully since only the relative thermodynamic stability of the different structures was considered, they are in good agreement with the experimental results and also support the competition between the (*N*,*N*) and the (*N*,*S*) palladium chelation.

Therefore, a bis(thiazoline), which can be either a C_2-symmetric *N*,*N*- or *S*,*S*-ligand or a C_1-symmetric *N*,*S*-ligand, is a particular type of ligand, which can open the way to new catalytic reactions in which the choice of the metal will direct the selection of the chelating heteroatom. Thus, thiazoline ligands should not be considered as simple oxazoline analogues, and the specific properties of sulfur, which is able to coordinate soft metals unlike oxygen, need to be taken into account.

4. Computational methods

All-electron calculations were performed with the quantum chemical program package Turbomole [19] employing either the BP86 functional [20,21] in combination with the resolution-of-the-identity ('RI') density fitting technique or the B3LYP functional [22,23]. For the palladium atom, an effective core potential of the Stuttgart group was employed (which also accounts for the scalar relativistic effects) [24]. This potential includes 28 electrons of the inner shells, i.e. the 18 electrons belonging to the 4s, 4p, 4d and 5s shell are treated explicitly. While BP86/RI was used for all structure optimizations, B3LYP calculations were only performed for single points i.e. for the BP86/RI optimized structures. We used the TZVP basis by Schäfer et al. [25] throughout, which features a valence triple-zeta basis set with polarization functions on all atoms. For the calculations of charges, the natural population analyses from GAUSSIAN03 [26] was used. Solvent effects on the relative energies of the Pd-complexes investigated in this work may not be negligible. In order to assess the role of solvent effects we employed a continuum model – namely the COSMO model – to account for a CH_2Cl_2 environment. These calculations have been carried out for the **1a** series with the default COSMO parameters of the TURBOMOLE/COSMO implementation. The optimized atomic COSMO radii of ref. [27] have been used in combinations with non-optimized radii of 2.28 Å for palladium atoms [28]. As a result of the COSMO solvation, the relative energies of the complexes **1a-B**$_1$, **B**$_2$, *C* were reduced by 3–4 kJ/mol compared to **1a-A**. Hence, the energetical ordering of the different structures is unchanged and the qualitative picture is the same as in the case of the isolated structures (in vacuum). Therefore, all energies reported here are given for the generic complex structures in vacuum. Molecular structures were visualized with the program Molden [29].

5. Experimental

5.1. General

The reactions were carried out under nitrogen atmosphere unless stated otherwise and monitored by TLC using silica plates 60 F254 (Merck). Solvents were used in RPE grade (Carlo Erba) without further purification except for the reactions involving *t*-BuLi and Grignard reagents. In these cases, solvents were purified with a PURESOLV SPS400 apparatus developed by Innovative Technology Inc. Column chromatography was performed on silica gel Si 60 (40–63 μm) from Merck. *tert*-Butyllithium was titrated prior to use according to a described procedure [30]. NMR spectra were recorded on a Bruker DRX400 spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane with residual solvent signal used as an internal standard, coupling constants are

indicated in Hz. Splitting patterns are designated as: s = singlet, d = doublet, t = triplet, q = quartet, sept, dd = doublet of doublets, m = multiplet, and br = broad. IR spectra were measured on a Perkin–Elmer 16 PC FT-IR instrument. Mass spectra were recorded on a Waters Q-TOF micro by electrospray ionization (ES-MS). Optical rotation values $[\alpha]_D^{20}$ were measured on a Perkin–Elmer 241 polarimeter and are given in $10^{-1}{}^{\circ}$ cm^2 g^{-1}, *c* in g 100 ml^{-1}.

5.2. Synthesis of non-symmetric bis(thiazolines) (**3a** and **3b**)

They were prepared according to the general procedure previously described for C_2-symmetric bis(thiazolines) [3a], in five steps starting from isopropyl methyldithioester **5**, and using two different aminoalcohols in the two thioacylation steps.

5.2.1. (S_{Et},$S_{t\text{-}Bu}$)-4-tert-Butyl-2-[1-methyl-1-(4-ethyl-4,5-dihydro)thiazolyl]ethyl-2-thiazoline (**3a**)

Complex **3a** was prepared according to the general procedure, using as aminoalcohols (*S*)-(+)-2-amino-1-butanol and (*S*)-(+)-*tert*-leucinol. Purification by chromatography on silica gel (Et_2O/pentane: 20/80, R_f = 0.48 in UV) afforded the product as an orange oil (496 mg, 1.57 mmol). Overall yield: 35%. $[\alpha]_D^{20}$ −128 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (s, 9H, C(C*H*$_3$)$_3$), 1.00 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 1.53 (s, 3H, C(C*H*$_3$)$_2$), 1.54 (s, 3H, C(C*H*$_3$)$_2$), 1.59–1.84 (m, 2H, C*H*$_2$CH$_3$), 2.96 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 7.0 Hz, 1H, SC*H*HCHEt), 3.08 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 9.8 Hz, 1H, SC*H*HCH*t*-Bu), 3.19 (dd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 9.1 Hz, 1H, SCH*H*CH*t*-Bu), 3.32 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, SCH*H*CHEt), 4.18 (dd, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 9.8 Hz, 1H, C*H*t-Bu), 4.37–4.47 (m, 1H, C*H*Et). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 10.8 (CH$_2$CH$_3$), 26.7 (C(CH$_3$)$_2$), 26.85 (C(*C*H$_3$)$_3$), 26.90 (C(*C*H$_3$)$_2$), 27.6 (*C*H$_2$CH$_3$), 34.4 (SCH$_2$CH*t*-Bu), 35.5 (*C*(CH$_3$)$_3$), 37.7 (SCH$_2$CHEt), 47.5 (*C*(CH$_3$)$_2$), 78.4 (*C*HEt), 87.0 (*C*Ht-Bu), 172.6 (*C*NCH*t*-Bu), 173.9 (*C*NCHEt). IR (cm^{-1}): 2958, 2933, 2868, 1614, 1463, 1363, 1220, 1057, 994, 880. TOF MS ES$^+$ [M+H]$^+$ Calc. for $C_{15}H_{27}N_2S_2$: 299.1616; Found: 299.1621. ES-MS *m*/*z* (%): 299 (M+H, 32), 211 (100), 183 (78), 129 (5), 89 (21), 83 (23). Elemental Anal. Calc. for $C_{15}H_{26}N_2S_2$: C, 60.35; H, 8.78; N, 9.38. Found: C, 60.20; H, 8.96; N, 9.12%.

5.2.2. (R_{Et},$S_{t\text{-}Bu}$)-4-tert-Butyl-2-[1-methyl-1-(4- ethyl-4,5-dihydro)thiazolyl]ethyl-2-thiazoline (**3b**)

Complex **3b** was prepared according to the general procedure, using as aminoalcohols (*R*)-(−)-2-amino-1-butanol and (*S*)-(+)-*tert*-leucinol. Purification by chromatography on silica gel (Et_2O/pentane: 20/80, R_f = 0.60 in UV) afforded the product as an orange oil (591 mg, 1.98 mmol). Overall yield: 34%. $[\alpha]_D^{20}$+9 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (s, 9H, C(C*H*$_3$)$_3$), 0.99 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 1.53 (s, 3H, C(C*H*$_3$)$_2$), 1.55 (s, 3H, C(C*H*$_3$)$_2$), 1.59–1.85 (m, 2H, C*H*$_2$CH$_3$), 2.96 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, SC*H*HCHEt), 3.08 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 9.9 Hz, 1H, SC*H*HCH*t*-Bu), 3.20 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 9.0 Hz, 1H, SCH*H*CH*t*-Bu), 3.33 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.5 Hz, 1H, SCH*H*CHEt), 4.18 (dd, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 9.8 Hz, 1H, C*H*t-Bu), 4.40–4.47 (m, 1H, C*H*Et). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 10.8 (CH$_2$CH$_3$), 26.6 (C(CH$_3$)$_2$), 26.9 (C(CH$_3$)$_3$), 27.0 (C(CH$_3$)$_2$), 27.7 (CH$_2$CH$_3$), 34.4 (SCH$_2$CH*t*-Bu), 35.5 (*C*(CH$_3$)$_3$), 37.8 (SCH$_2$CHEt), 47.5 (*C*(CH$_3$)$_2$), 78.5 (*C*HEt), 87.1 (*C*Ht-Bu), 172.5 (*C*NCH*t*-Bu), 173.9 (*C*NCHEt). IR (cm^{-1}): 2959, 2933, 2869, 1615, 1463, 1363, 1219, 1057, 994, 880. TOF MS ES$^+$ [M+H]$^+$ Calc. for $C_{15}H_{27}N_2S_2$: 299.1616; Found: 299.1626. ES-MS *m*/*z* (%): 299 (M+H, 18), 211 (100), 183 (58), 89 (11), 83 (12).

5.3. Synthesis of non-symmetric bis(thiazolines) (**3c** and **3d**)

They were prepared according to the general procedure previously described for C_2-symmetric bis(thiazolines) [3a], starting from isopropyl methyldithioester **5**, using for the first thioacylation as aminoalcohols (*R*)-(−)-2-amino-1-butanol and (*S*)-(+)-*tert*-leucinol, respectively. In these cases (formation of unsubstituted thiazoline), the thiazoline-dithioester **11** was reacted with 2-bromoethylamine hydrobromide and thioacylation and cyclisation take place in one-step (this step is detailed below for **3c**).

5.3.1. (R)-4-Ethyl-2-[1-methyl-1-(4,5-dihydro)thiazolyl]ethyl-2-thiazoline (**3c**)

2-Bromoethylamine hydrobromide (209 mg, 1.01 mmol) was suspended in THF (2 mL) and deprotonated with triethylamine (0.14 mL, 102 mg, 1.01 mmol) at 0 °C. The ice bath was removed and a solution of (*R*)-methyl-2-methyl-2-(4-ethyl-4,5-dihydro)thiazolyl-propanedithioate (250 mg, 1.01 mmol) in THF (1 ml) was slowly added. The addition of two further equivalents of NEt_3 was performed after 30 min. The mixture was stirred over night, filtered and solvents evaporated. Purification by chromatography on silica gel (Et_2O/pentane: 50/50, R_f = 0.30 in UV) afforded the product as a pale yellow oil (185 mg, 0.76 mmol). Overall yield: 40%. $[\alpha]_D^{20}$ +76 (*c* 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (t, $^3J_{HH}$ = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 1.55 (s, 3H, C(C*H*$_3$)$_2$), 1.56 (s, 3H, C(C*H*$_3$)$_2$), 1.58–1.85 (m, 2H, C*H*$_2$CH$_3$), 2.97 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 7.1 Hz, 1H, SC*H*HCHEt), 3.27 (t, $^3J_{HH}$ = 8.4 Hz, 2H, SC*H*$_2$CH$_2$), 3.34 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, SCH*H*CHEt), 4.25 (t, $^3J_{HH}$ = 8.4 Hz, 2H, SCH$_2$C*H*$_2$), 4.41–4.48 (m, 1H, C*H*Et). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 10.8 (CH$_2$CH$_3$), 26.7 (C(CH$_3$)$_2$), 26.8 (C(*C*H$_3$)$_2$), 27.7 (*C*H$_2$CH$_3$), 34.0 (SCH$_2$CH$_2$), 37.7 (SCH$_2$CHEt), 47.4 (*C*(CH$_3$)$_2$), 64.7 (SCH$_2$*C*H$_2$), 78.6 (*C*HEt), 173.5 (*C*NCHEt), 176.0 (*C*NCH$_2$). IR (cm^{-1}): 2962, 2931, 2854, 1611, 1461, 1383, 1363, 1223, 1048, 988, 880, 713. TOF MS ES$^+$ [M+H]$^+$ Calc. for $C_{11}H_{19}N_2S_2$: 243.0990; Found: 243.0991. ES-MS *m*/*z* (%): 243 (M+H, 36), 183 (15), 155 (100), 128 (3).

5.3.2. (S)-4-tert-Butyl-2-[1-methyl-1-(4,5-dihydro)thiazolyl]-ethyl-2-thiazoline (**3d**)

Was prepared according to the general procedure. Purification by chromatography on silica gel (Et_2O/pentane: 30/70, R_f = 0.30 in UV) afforded the product as a pale yellow oil (254 mg, 0.94 mmol). Overall yield: 30%. $[\alpha]_D^{20}$ −71 (*c* 0.95, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.99 (s, 9H, C(C*H*$_3$)$_3$), 1.54 (s, 3H, C(C*H*$_3$)$_2$), 1.56 (s, 3H, C(C*H*$_3$)$_2$), 3.09 (dd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 9.8 Hz, 1H, SC*H*HCH*t*-Bu), 3.21 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 9.1 Hz, 1H, SCH*H*CH*t*-Bu), 3.26 (t, $^3J_{HH}$ = 8.3 Hz, 2H, SC*H*$_2$CH$_2$), 4.19 (dd, $^3J_{HH}$ = 9.1 Hz, $^3J_{HH}$ = 9.8 Hz, 1H, C*H*t-Bu), 4.25 (t, $^3J_{HH}$ = 8.3 Hz, 2H, SCH$_2$C*H*$_2$). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 26.6 (C(*C*H$_3$)$_2$), 26.8 (C(*C*H$_3$)$_3$), 26.9 (C(CH$_3$)$_2$), 34.1 (SCH$_2$CH$_2$), 34.4 (SCH$_2$CH*t*-Bu), 35.5 (*C*(CH$_3$)$_3$), 47.5 (*C*(CH$_3$)$_2$), 64.6 (SCH$_2$*C*H$_2$), 87.1 (*C*Ht-Bu), 172.4 (*C*NCH*t*-Bu), 176.2 (*C*NCH$_2$). IR (cm^{-1}): 2954, 2866, 1614, 1464, 1363, 1222, 1058, 1022, 992, 929, 880, 720. TOF MS ES$^+$ [M+H]$^+$ Calc.: for $C_{13}H_{23}N_2S_2$: 271.1303; Found: 271.1316. ES-MS *m*/*z* (%): 271 (M+H, 18), 211 (25), 155 (100), 128 (13), 83 (26). Elemental Anal. Calc. for $C_{13}H_{22}N_2S_2$: C, 57.73; H, 8.20; N, 10.36; Found: C, 58.12; H, 8.48; N, 10.62%.

5.4. Synthesis of oxazoline–thiazolines (**4a**–**4c**)

They were prepared in five steps starting from isobutyric acid chloride **6**, and using two different aminoalcohols in the acylation, then in the thioacylation step. Starting from oxazolines **10** (see their general synthesis below) instead of thiazolines **9**, the same general procedure previously described for bis(thiazolines) was used.

5.4.1. (R,R)-4-Ethyl-2-[1-methyl-1-(4-ethyl-4,5-dihydro)-oxazolyl]ethyl-2-thiazoline (**4a**)

Complex **4a** was prepared according to the general procedure from oxazoline **10a** using in the thioacylation step (*R*)-(−)-2-ami-

no-1-butanol. Purification by chromatography on silica gel (Et_2O/pentane: 30/70, R_f = 0.10 in UV) afforded the product as yellow oil (70 mg, 0.28 mmol). Overall yield: 17%. $[\alpha]_D^{20}$ +108(*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (t, $^3J_{HH}$ = 7.4 Hz, 3H, OCNCHCH$_2$C*H*$_3$), 0.97 (t, $^3J_{HH}$ = 7.4 Hz, 3 H, SCNCHCH$_2$C*H*$_3$), 1.49–1.81 (m, 4H, 2 × C*H*$_2$CH$_3$), 1.51 (s, 6H, C(C*H*$_3$)$_2$), 2,95 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 7.1 Hz, 1H, SC*H*H), 3.33 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, SCH*H*), 3.91 (t, 1H, OC*H*H), 4.02–4.10 (m, 1H, OCNC*H*Et), 4.27 (dd, $^2J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, OCH*H*), 4.39–4.46 (m, 1H, SCNC*H*Et). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 9.7 (CH$_2$CH$_3$), 10.7 (CH$_2$*C*H$_3$), 25.58 (C(*C*H$_3$)$_2$), 25.62 (C(*C*H$_3$)$_2$), 27.8 (*C*H$_2$CH$_3$), 28.2 (*C*H$_2$CH$_3$), 37.7 (S*C*H$_2$), 43.1 (*C*(CH$_3$)$_2$), 67.2 (OCNCHEt), 72.4 (O*C*H$_2$), 78.5 (SCN*C*HEt), 169.6 (O*C*N), 172.7 (S*C*N).

5.4.2. (R,S)-4-Ethyl-2-[1-methyl-1-(4-ethyl-4,5-dihydro)-oxazolyl]ethyl-2-thiazoline (**4b**)

Was prepared according to the general procedure from oxazoline **10a** using in the thioacylation step (*S*)-(+)-2-amino-1-butanol. Purification by chromatography on silica gel (Et_2O/pentane: 50/50, R_f = 0.22 in UV) afforded the product as yellow oil (546 mg, 2.15 mmol). Overall yield: 23%. $[\alpha]_D^{20}$ −5.8 (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.92 (t, $^3J_{HH}$ = 7.4 Hz, 3H, OCNCHCH$_2$C*H*$_3$), 0.98 (t, $^3J_{HH}$ = 7.4 Hz, 3H, SCNCHCH$_2$C*H*$_3$), 1.50–1.82 (m, 4H, 2x C*H*$_2$CH$_3$), 1.52 (s, 6H, C(C*H*$_3$)$_2$), 2,96 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 7.1 Hz, 1H, SC*H*H), 3.34 (dd, $^2J_{HH}$ = 10.8 Hz, $^3J_{HH}$ = 8.6 Hz, 1H, SCH*H*), 3.92 (t, 1H, OC*H*H), 4.03–4.11 (m, 1H, OCNC*H*Et), 4.29 (dd, $^2J_{HH}$ = 9.3 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, OCH*H*), 4.40–4.47 (m, 1H, SCNC*H*Et). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 9.7 (CH$_2$CH$_3$), 10.7 (CH$_2$ *C*H$_3$), 25.5 (C(*C*H$_3$)$_2$), 25.8 (C(*C*H$_3$)$_2$), 27.8 (*C*H$_2$CH$_3$), 28.2 (*C*H$_2$CH$_3$), 37.7 (S*C*H$_2$), 43.1 (*C*(CH$_3$)$_2$), 67.3 (OCNCHEt), 72.4 (O*C*H$_2$), 78.5 (SCN*C*HEt), 169.6 (O*C*N), 172.7 (S*C*N). IR (cm^{-1}): 2962, 2933, 2876, 1661, 1620, 1133, 1029, 981, 958, 922, 754. TOF MS ES$^+$ [M+H]$^+$ Calc. for $C_{13}H_{23}N_2OS$: 255.1531; Found: 255.1538. ES-MS *m*/*z* (%): 255 (M+H, 29), 183 (28), 167 (100), 156 (2), 125 (5), 113 (2), 89 (13).

5.4.3. (S,S)-4-tert-Butyl-2-[1-methyl-1-(4-tert-butyl-4,5-dihydro)oxazolyl]ethyl-2-thiazoline (**4c**)

Complex **4a** was prepared according to the general procedure from oxazoline **10b** using in the thioacylation step (*S*)-(+)-*tert*-leucinol. Purification by chromatography on silica gel (Et_2O/pentane: 20/80, R_f = 0.29 in UV) afforded the product as yellow oil (76 mg, 0.24 mmol). Overall yield: 20%. $[\alpha]_D^{20}$ −89 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (s, 9H, C(C*H*$_3$)$_3$), 0.95 (s, 9H, C(C*H*$_3$)$_3$), 1.516 (s, 3H, C(C*H*$_3$)$_2$), 1.520 (s, 3H, C(C*H*$_3$)$_2$), 3.08 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 9.3 Hz, 1H, SC*H*H), 3.20 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 9.2 Hz, 1H, SCH*H*), 3.84 (dd, $^2J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, OCNC*H*t-Bu), 4.08 (dd, $^2J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 7.2, 1H, OC*H*H), 4.15 (dd, $^2J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 10.1 Hz, 1H, OCH*H*), 4.20 ("t", $^3J_{HH}$ = 9.2 Hz, 1H, SCNC*H*t-Bu). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 25.78 (C(*C*H$_3$)$_2$), 25.82 (C(*C*H$_3$)$_2$), 26.0 (OCNCHC(*C*H$_3$)$_3$), 26.7 (SCNCHC(*C*H$_3$)$_3$), 34.1 (*C*(CH$_3$)$_3$), 34.2 (S*C*H$_2$), 35.5 (*C*(CH$_3$)$_3$), 43.3 (*C*(CH$_3$)$_2$), 69.1 (O*C*H$_2$), 75.5 (OCNC*H*t-Bu), 86.9 (SCNC*H*t-Bu), 169.4 (O*C*N), 171.8 (S*C*N). IR (cm^{-1}): 2954, 2869, 1666, 1627, 1466, 1364, 1130, 979, 925, 755. TOF MS ES+ [M+H]$^+$ Calc. for $C_{17}H_{31}N_2OS$: 311.2157; Found:311.2156. ES-MS *m*/*z* (%): 311 (M+H, 67), 211 (100), 195 (68), 117 (3).

5.5. General synthesis of oxazolines (**10**)

Were prepared in two steps (amide synthesis and intramolecular cyclisation) starting from 2-methyl-propanoylchloride and an aminoalcohol.

Amide synthesis: The corresponding aminoalcohol (1 equiv.) and triethylamine (1.1 equiv.) were dissolved in dry dichloromethane (*c* = 0.2 M). After dropwise addition of 2-methyl-propanoylchloride (1 equiv.), the solution was stirred 3 h, then filtered over silica (eluent: EtOAc). Evaporation of solvents afforded the products as white solids.

5.5.1. (R)-N-(1-Hydroxymethyl)propyl-2-methyl-propaneamide (**8a**)

Was prepared using (*R*)-(−)-2-amino-1-butanol as aminoalcohol. Yield: 4.54 g (28.5 mmol, 95%). R_f = 0.30 (EtOAc, blue in PMA). M.p. 70 °C. $[\alpha]_D^{20}$ +44 (*c* 0.95, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (t, $^3J_{HH}$ = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 1.16 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 1.17 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 1.42–1.66 (m, 2H, C*H*$_2$CH$_3$), 2.38 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 2.60 (br, 1H, O*H*), 3.58 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.8 Hz, 1H, C*H*HOH), 3.68 (dd, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 3.4 Hz, 1H, CH*H*OH), 3.80–3.88 (m, 1H, C*H*Et), 5.67 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 10.7 (CH$_2$*C*H$_3$), 19.7 (CH(*C*H$_3$)$_2$), 19.9 (CH(*C*H$_3$)$_2$), 24.3 (*C*H$_2$CH$_3$), 35.9 (*C*H(CH$_3$)$_2$), 53.4 (*C*HEt), 65.7 (CH$_2$OH), 178.3 (N*C*O). IR (cm^{-1}): 3278, 2967, 2932, 1641, 1542, 1236, 1101, 1046, 711. TOF MS ES$^+$ [M+H]$^+$ Calc. for $C_8H_{18}NO_2$: 160.1338; Found: 160.1342. ES-MS *m*/*z* (%): 160 (M+H, 60), 143 (21), 142 (5), 90 (100).

5.5.2. (S)-N-(1-Hydroxymethyl-2,2-dimethyl)propyl-2-methyl-propaneamide (**8b**)

Was prepared using (*S*)-(+)-*tert*-leucinol as aminoalcohol. Yield: 1.29 g (6.9 mmol, 86%). R_f = 0.35 (EtOAc, blue in PMA). M.p. 124 °C. $[\alpha]_D^{20}$ −18 (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (s, 9H, C(C*H*$_3$)$_3$), 1.17 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 1.18 (d, $^3J_{HH}$ = 6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 2.43 (sept, $^3J_{HH}$ = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 3.51–3.57 (m, 1H, C*H*HOH), 3.79–3.87 (m, 1 + 1H, CH*H*OH and C*H*t-Bu), 5.67 (br, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 19.7 (CH(*C*H$_3$)$_2$), 20.1 (CH(*C*H$_3$)$_2$), 27.1 (C(*C*H$_3$)$_3$), 33.6 (*C*(CH$_3$)$_3$), 36.1 (*C*H(CH$_3$)$_2$), 59.4 (*C*Ht-Bu), 63.5 (*C*H$_2$OH), 178.6 (N*C*O). IR (cm^{-1}): 3282, 2966, 1649, 1557, 1369, 1267, 1238, 1051, 910. TOF MS ES$^+$ [M+H]$^+$ calcd. for $C_{10}H_{22}NO_2$: 188.1651; Found: 188.1655. ES-MS *m*/*z* (%): 188 (M+H, 70), 118 (100), 100 (21), 83 (18).

Cyclisation: To a solution of PPh_3 (1.5 equiv.) in dry THF (*c* = 0.5 M as to the amide concentration), DEAD (1.5 equiv.) was added dropwise and the solution was stirred 40 min at 20 °C. The corresponding amide (1 equiv.) was introduced in several portions and the mixture was allowed to react for 24 h. After filtration of the precipitate, solvents were evaporated to about a forth of the original volume and the mixture was poured onto the same amount of pentane. Filtration, evaporation of solvents and column chromatography yielded the oxazolines as colourless oils.

5.5.3. (R)-4-Ethyl-2-isopropyl-2-oxazoline (**10a**)

Was prepared from amide **8a**. Yield: 1.99 g (14.1 mmol, 59 %). R_f = 0.14 (Et_2O/pentane: 10/90, green in PMA). $[\alpha]_D^{20}$ +79 (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (t, $^3J_{HH}$ = 7.4 Hz, 3 H, CH$_2$C*H*$_3$), 1.18 (d, $^3J_{HH}$ = 7.0 Hz, 6 H, CH(C*H*$_3$)$_2$), 1.42–1.69 (m, 2H, C*H*$_2$CH$_3$), 2.56 (septet, $^3J_{HH}$ = 7.0 Hz, 1H, C*H*(CH$_3$)$_2$), 3.82–3.86 (m, 1H, OC*H*H), 3.97–4.04 (m, 1H, C*H*Et), 4.25 (dd, 1H, $^2J_{HH}$ = 9.4 Hz, $^3J_{HH}$ = 8.1 Hz, OCH*H*). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 9.8 (CH$_2$*C*H$_3$), 19.9 (CH(*C*H$_3$)$_2$), 20.0 (CH(*C*H$_3$)$_2$), 28.3 (*C*H(CH$_3$)$_2$), 28.6 (*C*H$_2$CH$_3$), 67.2 (*C*HEt), 71.8 (O*C*H$_2$), 171.7 (O*C*N). IR (cm^{-1}): 2969, 2935, 2878, 1665, 1463, 1199, 1147, 982, 920. TOF MS ES$^+$[M+H]$^+$ Calc. for $C_8H_{16}NO$: 142.1232; Found: 142.1225. ES-MS *m*/*z* (%): 142 (M+H, 100), 126, 98, 88.

5.5.4. (S)-4-tert-Butyl-2-isopropyl-2-oxazoline (**10b**)

Was prepared from amide **8b**. Yield: 438 mg (2.59 mmol, 55%). R_f = 0.20 (Et_2O/pentane: 10/90, green in PMA). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.87 (s, 9H, C(C*H*$_3$)$_3$), 1.18 (d, $^3J_{HH}$ = 7.0 Hz, 3H, CH(C*H*$_3$)$_2$), 1.19 (d, $^3J_{HH}$ = 7.0 Hz, 3H, CH(C*H*$_3$)$_2$), 2.61 (septet, $^3J_{HH}$ = 7.0 Hz, 1H, C*H*(CH$_3$)$_2$), 3.80 (dd, $^3J_{HH}$ = 10.0 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, C*H*t-Bu), 4.04 (dd, 1H, $^2J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 7.2 Hz, OC*H*H), 4.12 (dd, $^2J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 10.0 Hz, 1H, OCH*H*). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 20.0 (CH(*C*H$_3$)$_2$), 20.1 (CH(*C*H$_3$)$_2$), 25.8 (C(*C*H$_3$)$_3$), 28.4 (*C*H(CH$_3$)$_2$), 33.8 (*C*(CH$_3$)$_3$), 68.5 (O*C*H$_2$), 75.4 (*C*Ht-Bu), 171.5 (O*C*N).

5.5.5. Typical procedure for the Pd-catalyzed allylic substitution

(*E*)-1,3-Diphenyl-2-propenyl acetate (156 mg, 0.62 mmol), ligand (6 mol%, 0.04 mmol), allylpalladium chloride dimer (6 mg, 2.5 mol%, 0.02 mmol) and potassium acetate (3 mg, 5 mol%, 0.03 mmol) were introduced into a Schlenk flask and 2 mL of dicholormethane was added. The mixture was stirred for 20 min before the successive addition of dimethyl malonate (0.21 mL, 1.86 mmol) and *N,O*-bis(trimethylsilyl)acetamide (BSA) (0.49 mL, 1.86 mmol). The mixture was stirred at room temperature and monitored by TLC (SiO_2, Et_2O/pentane: 20/80). After completion, solvents were evaporated, the residue dissolved in ether and filtered (syringe filter). After evaporation of ether, the residue was analysed by HPLC using a Daicel Chiralpak AD analytical column (*n*-heptane/2-propanol: 90/10, flow rate: 1 mL/min, 251.0 nm). Enantiomeric excess of (*E*)-2-methoxycarbonyl-3,5-diphenylpent-4-enoate was measured by HPLC; the separation of the two enantiomers was calibrated with racemic product: (*R*)-enantiomer, t_1 = 12.4 min; (*S*)-enantiomer, t_2 = 17.4 min.

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