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Tetrahedron 60 (2004) 9263–9272
Tetrahedron

Chiral thiazoline ligands: application in Pd-catalysed allylic substitution

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Received 7 May 2004; revised 1 July 2004; accepted 22 July 2004

Available online 26 August 2004

Abstract—A series of thiazoline ligands, analogues of well-known oxazolines, easily prepared from chiral aminoalcohols and appropriate dithioesters, was tested in the Pd-catalysed allylic substitution. A systematic comparison with the corresponding oxazolines (using literature data or our own tests) has been made for each case. Some important differences (between their catalytic activity and enantioselectivity) were noted for the two types of ligands, especially in the case of bis(thiazolines) and bis(oxazolines).
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1. Introduction

In comparison with the widely applied oxazolines ligands in asymmetric catalysis[1], their sulfur analogues, the thiazolines, are less known and have been rarely used for this purpose. However, since the first example published by Helmchen[2] and which concerned the use of metal-complexes of chiral bis(thiazolines) as catalysts, the interest in thiazoline ligands seem to increase and other authors reported the syntheses and applications of new structures of these compounds.[3,4] Comparative studies,[2,4e] in some well known metal-catalysed asymmetric reactions between oxazolines and thiazolines, appear necessary for further development of the latter, bringing out the different behaviors of the two heterocycles towards metal chelation. However, studies related to the thiazoline ligands were limited so far by the difficult access to a large variety of enantiopure structures. In our previous work,[3] we described a versatile method to prepare thiazolines as easily as oxazolines by using chiral aminoalcohols and appropriate dithioesters (Scheme 1) together with a preliminary test using one of them in Pd-catalysed allylic substitution. We report here our full study on the efficiency, as ligands in this model reaction, of all the synthesized thiazolines (Fig. 1). A systematic comparison with the corresponding already known oxazolines has been made for each case.

Keywords: Thiazolines; Oxazolines; Chiral ligands; Asymmetric catalysis; Allylic substitution.

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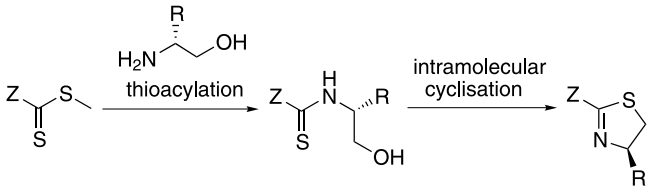
doi:10.1016/j.tet.2004.07.048

2. Results and discussion

2.1. Synthesis of thiazolines

The general syntheses of thiazolines **1**, **2**, **3**, **4** and **12** are already described in our previous paper,[3] starting from the corresponding dithioesters and commercial enantiopure aminoalcohols. The synthetic pathways used five steps (from the isopropyl or cyclohexyl dithioester) for the bis(thiazolines) **1** and **2** and two steps (from pyridyl or quinolyl dithioester) for the thiazolines **3**, **4** and **12**.[5] Two new types of structures have been added to the thiazoline ligand family and are reported here: the 8-quinolyl thiazolines **5** (Scheme 2), analogues of the reported 8-quinolyl oxazolines[6] and the phosphine-thiazoline **9b** (Scheme 3), analogue of the widely known phosphine-oxazoline.[7]

Similarly to the 2-quinolyl thiazolines, 8-quinolyl thiazolines **5** were prepared in two steps (with 81-86% overall yield) starting from the 8-quinolyl dithioester **13**[8] via the corresponding thioamides **14** (Scheme 2).



a: R = Et, **b**,**c**: R = iPr, **d**: R = tBu, **e**: R = Bn, **f**: R = Ph

Scheme 1.

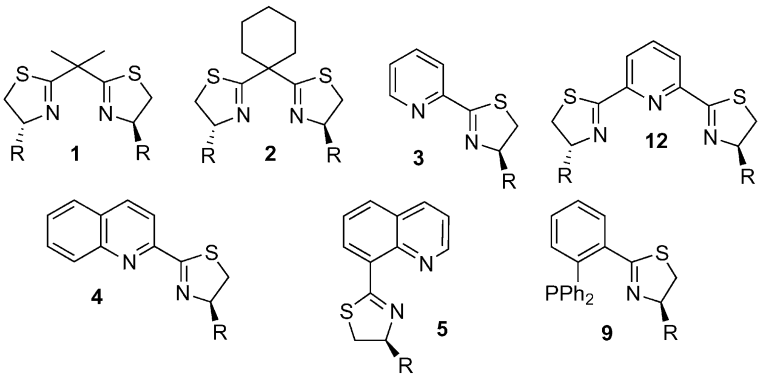
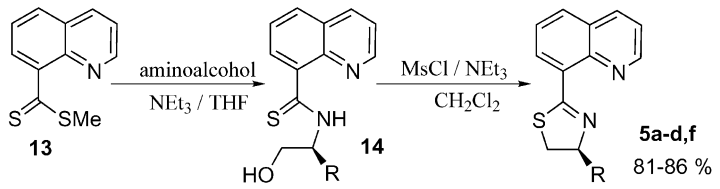
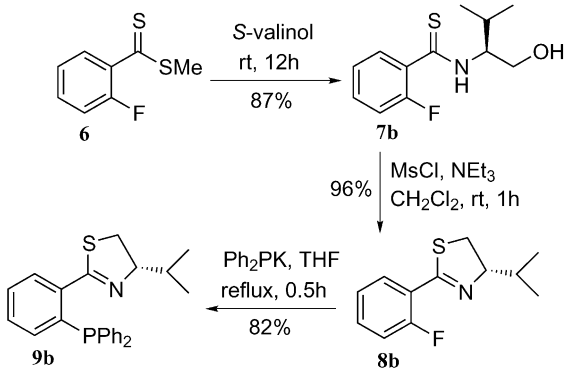


Figure 1.



Scheme 2.

Phosphine-thiazoline **9b** was prepared starting from the 2-fluoro-phenylthiazoline **8b** by reaction with potassium diphenylphosphide.[9] Thiazoline **8b** was obtained in two steps (thioacylation, then cyclization of **7b**) from 2-fluoro-benzene dithioester **6**[8] and *S*-valinol. The overall yield for the three steps was 68% (Scheme 3).

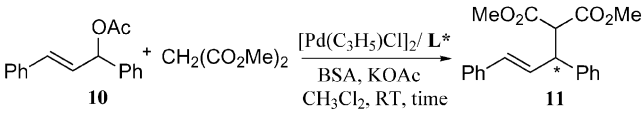


Scheme 3.

It should be noted that we recently reported a new high yielding method to synthesize all required aromatic and heteroaromatic dithioesters, precursors of thiazolines **3**, **4**, **5**, **8** and **12**[8] (Scheme 4).

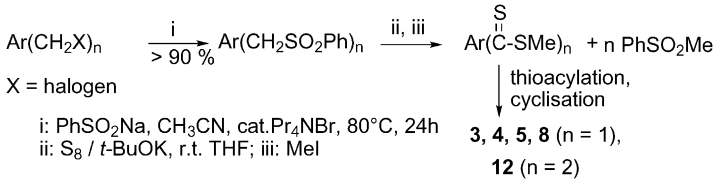
2.2. Pd-catalysed allylic substitution using thiazolines and comparison with oxazolines

We chose as a model reaction the version of the Pd-catalysed allylic substitution which is often used to test new ligands[10] the enantioselective substitution of the acetyloxy group of the racemic 1,3-diphenylpropenyl acetate **10** by the carbanion of the dimethyl malonate. The latter is generated using the couple bis(trimethylsilyl)-acetamide (BSA)/potassium acetate (KOAc), in presence of allylpalladium dimer. This affords the (*E*)-2-methoxycarbonyl-3,5-diphenylpent-4-enoate **11** (Scheme 5).



Scheme 5.

First, the effects of solvent (Et_2O, THF, CH_2Cl_2, toluene, CH_3CN), temperature (20, 0 °C, reflux of toluene or CH_2Cl_2) and amounts of reagents and catalyst were examined for each type of thiazoline ligand.[11] We selected and summarized here the results obtained under optimal conditions (CH_2Cl_2 at room temperature, see Section 3). The comparison with the corresponding oxazolines has



Scheme 4.

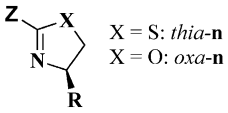


Figure 2.

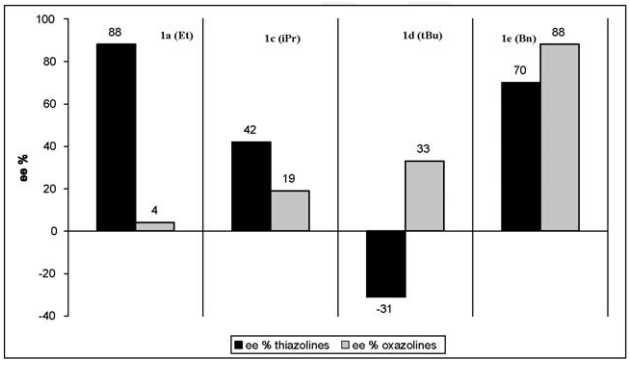
been made using literature data or our own experimental results.

In order to make easier the analysis of the following results, prefixes thia and oxa will be employed respectively for thiazolines and oxazolines ligands, the same number *n* indicating the analogy of their structures (Fig. 2).

Graphs 1 and 2 facilitate the comparison between the enantiomeric excesses obtained with the different ligands.

2.2.1. Bis(thiazolines) 1 and 2. In this series, all catalytic tests were done in our laboratory, except for oxa-**1e**, for which data were extracted from the literature.[12]

The analysis of Table 1 and Graph 1 discloses some amazing differences between the two types of ligands.

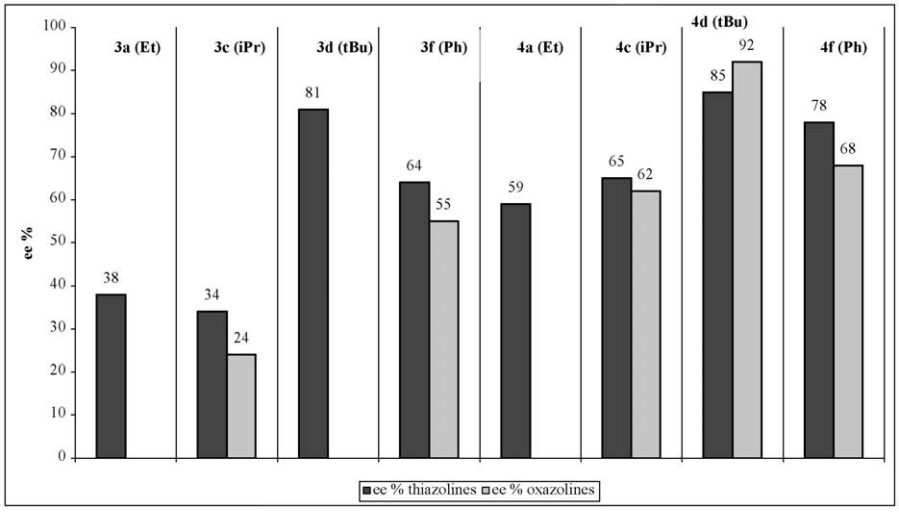


Graph 1. Comparative graph: ee % of **11** with ligands **1** (Table 1, entries 1, 2, 4–9); (*R*)-**11** ee % are given in positive values and (*S*)-**11** ee % in negative values; for an easier reading of the graph we extrapolated the data for the (*S,S*) ligands oxa and thia-**1d** and **1e** and considered them of (*R,R*) configuration).

Generally, bis(thiazolines) (Table 1, entries 1–4, 6–8) had better catalytic activity (see the reaction time) than the corresponding bis(oxazolines) and gave higher ee % for **11**. The only exception was found for the benzyl substituted ligand **1e** for which the results were nearly comparable, but favourable to oxa-**1e** (Table 1, entries 5 and 9). For most cases, enantiomer (*R*)-**11** was the major enantiomer obtained using ligands **1**[13] or **2** with (*R,R*) configuration, while (*S*)-**11** comes from (*S,S*) ligands **1** or **2**. One exception emerged for thia-**1d** with (*S,S*) configuration, which led to (*R*)-**11**. Moreover, in the case of bis(thiazolines), the enantiomeric excess of **11** decreases from thia-**1a** to thia-**1b**, with the increase of the steric hindrance of the substituent R on the heterocycle, leading even to an inversion of configuration in the case of thia-**1d**, when R = *t*Bu, in contrast to the bis(oxazolines) series (Graph 1).

A possible explanation for this specific behavior of bis(thiazolines) could be a competition between nitrogen and sulfur in the chelation of palladium.[4e] Indeed, compared to oxygen, sulfur, due to its voluminous HOMO orbital, is able to coordinate soft metals like Pd. Based on already described models,[12,14] we suggest the co-existence of three π-allylic palladium complexes (intermediates in the reaction mixture): the complex **A**-(**N,N**), in which Pd is chelated by the two nitrogen atoms and the two diastereomeric complexes **B1**-(**N,S**) *syn–syn* (*endo*) and **B2**-(**N,S**) *syn–syn* (*exo*), in which Pd is chelated by one nitrogen and one sulfur atoms (Scheme 6).

The reaction involving the complex **A**-(**N,N**) should proceed as for bis(oxazolines).[12,14] In this case, a strong interaction between the substituent R of one heterocycle and one phenyl group of the allylic substrate, directs the attack of the nucleophile preferentially on the more sterically congested carbon center (C^1 in Scheme 6) leading to a major (*R*) product for a (*R,R*) configuration of the ligand. It is possible that an important increase of the steric interaction in **A**-(**N,N**) (with a more bulky R substituent), causes a rotation of one of the thiazoline cycles, releasing the constraint and allowing the Pd-chelation by one sulfur atom to give **B1**-(**N,S**) complex. The C_2 symmetric bis(thiazoline)

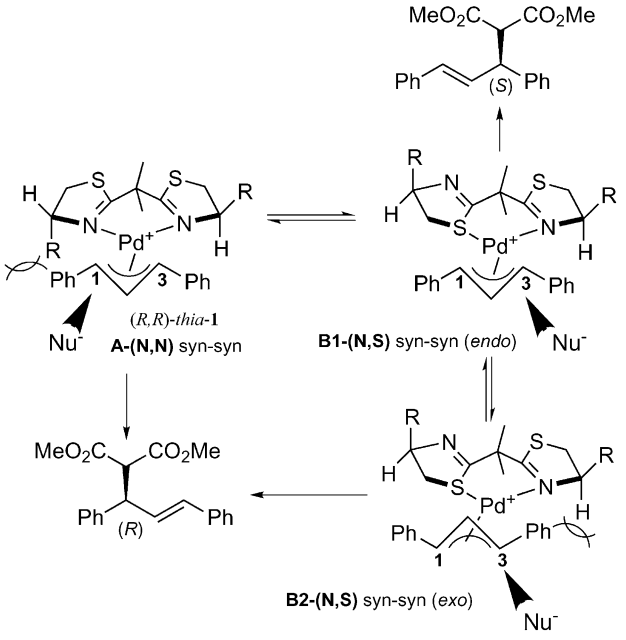


Graph 2. Comparative graph: ee% of **11** with ligands **3** (Table 2, entries 1, 2, 4–7) and **4** (Table 3, entries 1, 2, 4–8); (*R*)-**11** ee % are given in positive value) and for an easier reading of the graph we extrapolated the data for the (*S*) ligands and considered them of (*R,R*) configuration.

Table 1. Pd-catalysed asymmetric allylic substitution with bis(thiazolines) thia-**1** and **2** and bis(oxazolines) oxa-**1**

Entry	Ligand	Config. of the ligand	R	Time (h)	Conv. %	ee %	Config. of **11**
1	thia-**1a**	(*R*,*R*)	Et	30	95	88	(*R*)
2	thia-**1b**	(*S*,*S*)	*i*Pr	42	95	42	(*S*)
3	thia-**1c**	(*R*,*R*)	*i*Pr	42	95	42	(*R*)
4	thia-**1d**	(*S*,*S*)	*t*Bu	30	90	31	(*R*)
5	thia-**1e**	(*S*,*S*)	Bn	72	94	70	(*S*)
6	oxa-**1a**	(*R*,*R*)	Et	168	7	4	(*R*)
7	oxa-**1b**	(*S*,*S*)	*i*Pr	168	8	19	(*S*)
8	oxa-**1d**	(*S*,*S*)	*t*Bu	168	20	33	(*S*)
9[a]	oxa-**1e**	(*S*,*S*)	Bn	68	97	88	(*S*)
10	thia-**2a**	(*R*,*R*)	Et	48	95	51	(*R*)
11	thia-**2c**	(*R*,*R*)	*i*Pr	72	95	41	(*R*)

[a] Literature data.



Scheme 6.

could now behave as a heterofunctinal hemilabile N,S-ligand.[15] In this case, the Pd-complex could exist in two diastereomeric forms in equilibrium, **B1**-(**N**,**S**) *syn–syn* (*endo*) and **B2**-(**N**,**S**) *syn–syn* (*exo*), the selectivity of the nucleophilic attack being dependent upon the difference between their reactivities.[7d,16] Therefore, the ligand can be considered relatively similar to the α-sulfanyl oxazolines ligands reported by Williams[17,18] for which, on the π-allylic intermediate complexes, an attack *trans* to the sulfur atom (C^3 in Scheme 6) is observed. Thus, complex **B1**-(**N**,**S**) would lead to (*S*)-**11**, while **A**-(**N**,**N**) and **B2**-(**N**,**S**) to (*R*)-**11**, explaining the decrease of the enantiomeric excess, as well as the inversion of the enantioselection, with a bulkier R substituent. The possibility of the metal-chelation by two sulfur atoms cannot be completely excluded, but in that case, the chiral effect around the sulfur would be probably too small to generate enantioselectivity.

In order to examine the Pd-chelation with bis(thiazolines) and to rationalize the experimental results, we have undertaken to analyse some Pd-complexes with bis(thiazolines) and tried to obtain crystallographic analyses. First, we attempted to prepare the postulated reaction intermediates

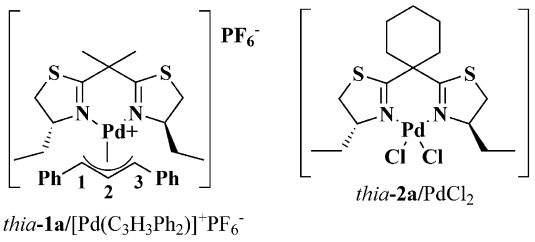


Figure 3.

thia-**1a**–**d**/$[Pd(C_3H_3Ph_2)]^+PF_6^-$ but, unfortunately, the complexes had low stability and crystals could not be isolated. However, one of them, the complex thia-**1a**/$[Pd(C_3H_3Ph_2)]^+PF_6^-$ (Fig. 3) could be characterized by ^1H NMR (see Section 3). The highest chemical shifts of the CH–N protons let supposed in this case the chelation of Pd by the two nitrogen atoms. The lack of the ^{13}C NMR did not allow us to have the $\Delta\delta(^{13}C)$ between the signals of C^1 and C^3, indicating the electronic difference around these atoms coordinated to Pd.[12a]

On the other hand, we succeeded in the isolation of a single crystal of the complex thia-**2a**/$PdCl_2$ (Fig. 3) and determined its structure by X-ray diffraction analysis.

The structure showed in Figure 4, clearly discloses the N,N coordination. However, this complex is not the real reaction intermediate, so it does not exclude our previous hypotheses related to the participation of sulfur in the chelation of the π-allylic palladium complex.

2.2.2. Pyridyl thiazolines 3. In this series, we have tested the thiazolines ligands and compared two of them with the corresponding oxazolines for which data have been already reported in the literature.[19]

The analysis of Table 2 shows that the catalytic activity of pyridyl oxazolines oxa-**3b**,**f** is better than that of their analogues thiazolines thia-**3b**,**f**. About 2 h are needed for the formers to give a good conversion, while 3–4 days are needed using the latters. Enantiomeric excesses are nearly similar, with a small superiority for the thiazolines (Table 2, Graph 2). The best result in the thiazolines series is 81% ee, obtained with thia-**3d** (R = *t*Bu).

The enantioselection was the same for both oxazolines and

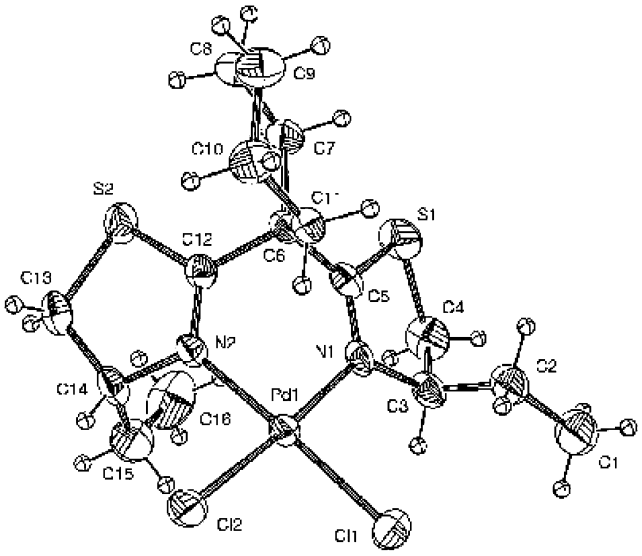
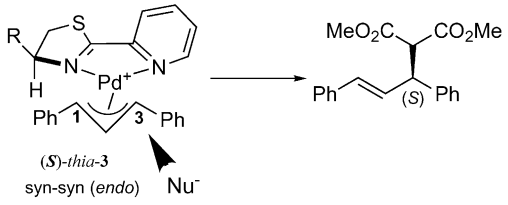


Figure 4.

thiazolines: the enantiomer (*R*)-**11** was obtained using ligands (*R*)-**3**, while (*S*)-**11** comes from (*S*)-**3**. This suggests that the reaction intermediates with thiazolines are similar to those proposed for the pyridyl oxazolines,[19] the Pd being complexed by the two nitrogen atoms of the pyridine and thiazoline heterocycles. Thus, the attack of the nucleophile should take place preferentially on the terminal carbon C[3] *trans* to the thiazoline nitrogen of the π-allylic Pd-complex *syn–syn endo*, for an *S* configuration of the ligand (Scheme 7).



Scheme 7.

2.2.3. 2,6-Pyridyl bis(thiazolines) 12. Only the (*S*,*S*)-2,6-pyridyl bis(thiazoline) **12b** (with R = *i*Pr) has been tested in this series. Whatever the conditions tested (different solvents and temperatures), the catalyst with this ligand proved to be completely inefficient in this reaction. The corresponding oxazoline (the Pybox) has been described giving 80% conversion after 2 days in refluxing dichloromethane and only 26% ee.[20] Besides, it is interesting to note that both oxazolines[21] and thiazolines[22] of this series have been successfully used as ligands in the cyclopropanation with diazoesters catalysed by ruthenium.

2.2.4. 2- and 8-Quinolyl thiazolines 4 and 5. The behavior of the 2-quinolyl thiazolines **4** as ligands in the allylic substitution was found to be very similar to that of the pyridyl thiazolines **3**. Their catalytic activity was found lower than the one of the pyridyl oxazolines reported in the literature.[19] Thus, about 72 to 144 h (Table 3, entries 1–5) are necessary for a good conversion using thiazolines, compared to 5 to 17 h (Table 3, entries 6–8) with the oxazoline analogues. Analysis of the results indicated in Table 3 (entries 1–8) and Graph 2 shows that the enantiomeric excesses are nearly similar and grow in this series with the steric hindrance of the R substituent. The best result was obtained in both cases with the most bulky substituent (R = *t*Bu), 85% ee with thia-**4d** and 92% ee with oxa-**4d**. The enantioselection for thia-**4d** was close to that observed for the corresponding pyridyl thiazoline thia-**3d** and let suppose a reaction intermediate similar in both cases (Scheme 7).

In a second series of experiments, we compared the 2-quinolyl thiazolines thia-**4** (Table 3, entries 1–5) and the 8-quinolyl thiazolines thia-**5** (Table 3, entries 9–12), which could form respectively with the Pd, a five- or a six-membered chelate ring. Then, the 8-quinolyl thiazolines thia-**5** were compared with the corresponding oxazolines[6]. The literature data show that for the quinolyl oxazolines, the 8-substituted derivatives oxa-**5** (Table 3, entries 13–15) are more reactive than the 2-substituted ones oxa-**4** (Table 3, entries 6–8). Compared to both 2-quinolyl thiazolines thia-**4** and their oxygenated analogues oxa-**5**, the 8-quinolyl thiazolines thia-**5** have been found to be rather inefficient, giving only 8–20% conversion after 10 days and 13–48% enantiomeric excesses.

2.2.5. 2-Diphenylphosphino-phenylthiazoline 9. Unlike the phosphine-oxazoline analogue, well known for its high efficiency as ligand in the Pd-catalysed allylic substitution,[7] thia-**9b** (R = *i*Pr) showed very disappointing results. Testing the two ligands in our reaction conditions (in dichloromethane at room temperature), a total conversion after 48 h and 93% ee were observed with the commercial oxa-**9b**, while only 8% conversion and 24% ee were obtained with thia-**9b**. Moreover, the enantioselection was reversed, the major enantiomer (*S*)-**11** being produced with (*S*)-oxa-**9b**, while (*R*)-**11** was preferentially obtained with (*S*)-thia-**9b** ligand.

In conclusion, a new family of ligands, the thiazolines, has

Table 2. Pd-catalysed asymmetric allylic substitution with pyridyl -thiazolines and -oxazolines **3**

Entry	Ligand	Config. of the ligand	R	Time (h)	Conv. %	ee %	Config. of **11**
1	thia-**3a**	(*R*)	Et	96	95	38	(*R*)
2	thia-**3b**	(*S*)	*i*Pr	96	95	34	(*S*)
3	thia-**3c**	(*R*)	*i*Pr	42	95	42	(*R*)
4	thia-**3d**	(*S*)	*t*Bu	30	90	81	(*S*)
5	thia-**3f**	(*R*)	Ph	72	94	64	(*R*)
6[a]	oxa-**3b**	(*S*)	*i*Pr	1	84	24	(*S*)
7[a]	oxa-**3f**	(*R*)	Ph	1.5	86	55	(*R*)

[a] Literature data.

Table 3. Pd-catalysed asymmetric allylic substitution with 2- and 8-quinolyl- thiazolines and oxazolines **4** and **5**

Entry	Ligand	Config. of the ligand	R	Time (h)	Conv. %	ee %	Config. of **11**
1	thia-**4a**	(*R*)	Et	144	95	59	(*R*)
2	thia-**4b**	(*S*)	*i*Pr	144	95	65	(*S*)
3	thia-**4c**	(*R*)	*i*Pr	96	95	66	(*R*)
4	thia-**4d**	(*S*)	*t*Bu	144	70	85	(*S*)
5	thia-**4f**	(*R*)	Ph	72	53	78	(*R*)
6[a]	oxa-**4b**	(*S*)	*i*Pr	4.5	88	62	(*S*)
7[a]	oxa-**4d**	(*S*)	*t*Bu	15	85	92	(*S*)
8[a]	oxa-**4f**	(*R*)	Ph	17	93	68	(*R*)
9	thia-**5a**	(*R*)	Et	240	19	13	(*R*)
10	thia-**5b**	(*S*)	*i*Pr	240	20	21	(*S*)
11	thia-**5d**	(*S*)	*t*Bu	240	15	22	(*S*)
12	thia-**5f**	(*R*)	Ph	240	8	48	(*R*)
13[a]	oxa-**5b**	(*S*)	*i*Pr	0.5	96	42	(*S*)
14[a]	oxa-**5d**	(*S*)	*t*Bu	1	88	77	(*S*)
15[a]	oxa-**5f**	(*R*)	Ph	2	94	59	(*R*)

[a] Literature data.

been tested in Pd-catalysed allylic substitution and the results were compared with those of the known oxazolines analogues. In several cases, the behavior of the two types of ligands was very different, as far as catalytic activities and enantiomeric excesses are concerned. Bis(thiazolines) were found to be globally more active than bis(oxazolines) and furnished good enantioselectivity (up to 88%). Pyridyl- and quinolyl-thiazolines were found to behave quite similarly to the corresponding oxazolines concerning the enantioselective induction, but were less active. Lastly, while the phosphine-oxazoline is one of the best ligands for this reaction, the phosphine-thiazoline was inefficient. In some cases, a competition between nitrogen and sulfur in the palladium chelation is suspected but further studies are still needed to confirm this hypothesis. Investigations related to other metal-catalyzed reactions are in progress, in our laboratory or in collaboration with other research groups, in order to expand the application scope of these thiazolines chiral ligands in asymmetric catalysis.

3. Experimental

3.1. General remarks

Most of the reactions were carried out under nitrogen atmosphere with magnetic stirring, unless otherwise specified and monitored by TLC using silica plates. Synthesized products were purified by flash column chromatography on silica gel or recrystallised if needed. Solvents were dried by distillation prior to use. The NMR spectra were recorded in $CDCl_3$, with a 'Brucker AC 250' or a 'Brucker AC 400' spectrometer. The chemical shifts δ are expressed in ppm, conventional abbreviations are used. Optical rotation values were measured on a Perkin–Elmer-241 polarimeter for the sodium D line at 20 °C. Melting points are uncorrected. The infrared spectra were recorded with a Perkin–Elmer 16 PC spectrometer, $\nu(cm^{-1})$ are given. Mass spectra were recorded with a Nermag R 10 10H spectrometer in electronic impact at 70 eV, *m*/*z* and relative abundance are given. HRMS were obtained with a JEOL JMS-AX 500 mass spectrometer. Elemental microanalyses were performed at Caen with an automatic apparatus CHNS-O ThermoQuest.

Compounds **1a**,**c** (**1b** is the enantiomer of **1c**); **2a**,**c**; **3a**,**c**,**f**; **4a**,**c**,**d**,**f** and **12d**,**f** have been already synthesized and characterized.[3]

3.2. Preparation of bis(thiazolines) 1d and 1e

Bis(thiazolines) **1d** and **1e** have been prepared using the general procedure described for bis(thiazolines),[3] in five steps, starting from isopropyl methyldithioester and the corresponding aminoalcohol (*S*-(+)-*tert*-leucinol and respectively *S*-(+)-phenylalaninol). They were purified by silica gel flash chromatography (pentane/diethyl ether: 70/30).

3.2.1. (*S*,*S*)-2,2′-(1-Methylethylidene)-bis[4,5-dihydro-4-*tert*-butylthiazole] 1d. Viscous yellow oil, $[\alpha]_D^{20} = -29$ (*c* 1, acetone), overall yield = 62%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.98 (s, 18H, 2×$(CH_3)_3C$), 1.52 (s, 6H, $C(CH_3)_2$), 3.10–3.16 (m, 4H, 2×CH_2S), 4.16 (t, 2H, *J* = 9.0 Hz, 2×CHN). ^{13}C NMR (62.9 MHz, $CDCl_3$): 26.3 (2×CH_3), 27.0 (2×CH_3), 27.1 (2×CH_3), 30.1 (2×$(CH_3)_3C$), 34.6 ($(CH_3)_2C$), 34.6 (2×CH_2), 47.8 ($C(CH_3)_2$), 87.3 (2×CHN), 173.1 (2×C=N). IR (NaCl): 2960, 2920, 2870, 1620 ($\nu_{C=N}$), 1450, 1370. Mass *m*/*z*: 326 (M^+, 15) 269 (100), 255 (17), 211 (8), 187 (6), 153 (41), 126 (13), 41 (12). Anal. Calcd for $C_{17}H_{30}N_2S_2$: C, 62.52; H, 9.26; N, 8.58. Found: C, 62.67; H, 9.45; N, 8.15.

3.2.2. (*S*,*S*)-2,2′-(1-Methylethylidene)bis[4,5-dihydro-4-benzylthiazole] 1e. yellow oil, overall yield = 58%. ^{1}H NMR (400 MHz, $CDCl_3$):1.58 (s, 6H, $C(CH_3)_2$), 2.73 (dd, 2H, *J* = 13.6, 9.3 Hz, 2×C*H*HPh), 3.06 (dd, 2H, *J* = 11.8, 5.4 Hz, 2×C*H*HS), 3.19 (dd, 2H, *J* = 13.6, 5.0 Hz, 2×CH*H*Ph), 3.22 (dd, 2H, *J* = 11.8, 6.0 Hz, 2×CH*H*S), 4.73–4.80 (m, 2H, 2×CHN), 7.22–7.34 (m, 10H, H^{arom}). ^{13}C NMR (62.9 MHz, $CDCl_3$): 26.9 ($C(CH_3)_2$), 37.8 (2×H_2C–Ph), 40.1 (2×CH_2S), 47.9 ($C(CH_3)_2$), 78.3 (2×CHN), 126.8 (2×CH^{arom}), 128.9 (2×CH^{arom}), 129.8 (2×CH^{arom}), 138.9 (2×C^{arom}), 174.9 (2×C=N). IR (NaCl): 3010, 2960, 2920, 1600 ($\nu_{C=N}$), 1450, 1350. Mass *m*/*z*: 394 (M^+, 18), 303 (100), 245 (2), 218 (2), 153 (45), 126 (12), 91 (25), 65 (7). Anal. Calcd for $C_{23}H_{26}N_2S_2$: C, 70.01; H, 6.64; N, 7.10. Found: C, 69.71; H, 6.32; N, 6.95.

3.3. Preparation of 2-pyridyl thiazoline 3d

Thiazoline **3d** has been prepared using the general procedure described for the 2-pyridyl thiazolines,[3] in two steps, starting from methyl pyridine-2-dithiocarboxylate[8] and *S*-*tert*-leucinol. It was purified by silica gel flash chromatography (pentane/diethyl ether: 70/30).

3.3.1. 2-[(*S*)-4,5-dihydro-4-*tert*-butyl-2-thiazolyl]pyridine 3d. Yellow solid, mp 44 °C, $[\alpha]_D^{20}=-51$ (*c* 1, acetone), overall yield=81%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.08 (s, 9H, $(CH_3)_3C$), 3.21 (dd, 1H, *J*=11.0, 10.4 Hz, C*H*HS), 3.33 (dd, 1H, *J*=11.0, 9.3 Hz, CH*H*S), 4.46 (dd, 1H, *J*=10.4, 9.3 Hz, CHN), 7.37 (dd, 1H, *J*=7.7, 4.9 Hz, H_4), 7.77 (dt, 1H, *J*=7.7, 1.4 Hz, H_5), 8.13 (d, 1H, *J*=7.7 Hz, H_6), 8.65 (dd, 1H, ^3J=4.9, 1.4 Hz, H_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): 27.2 ($(CH_3)_3C$), 33.4 (CH_2S), 35.8 ($(CH_3)_3C$), 88.8 (CHN), 122.0, 125.6, 136.7, 149.6, 151.8, 177.9 (SC=N) IR (NaCl): 2950, 2870, 1610 ($\nu_{C=N}$), 1460, 1380, 1270. Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71; S, 14.55. Found: C, 65.08; H, 7.40; N, 12.42; S, 14.33.

3.4. Preparation of pyridine-2,6-bis(thiazoline) 12b

Thiazoline **12b** has been prepared using the general method already described for analogous compounds with R=*t*Bu, Ph,[3] in two steps, starting from dimethyl 2,6-pyridine bis(dithiocarboxylate)[8] and two equivalents of *S*-valinol. It was purified by silica gel flash chromatography (pentane/diethyl ether).

3.4.1. 2,6-Bis[(*S*)-4,5-dihydro-4-isopropyl-2-thiazolyl]-pyridine 12b. Yellow solid, mp 190 °C, $[\alpha]_D^{20}=-125$ (*c* 1, acetone), overall yield=61%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.08 (t, 12H, *J*=6.7, Hz, 2×$CH(CH_3)_2$), 2.13 (oct, 2H, *J*=6.7 Hz, 2×C*H*$(CH_3)_2$), 3.11 (t, 2H, *J*=10.4 Hz, 2×C*H*HS), 3.38 (dd, 2H, *J*=10.4, 9.3 Hz, 2×C*H*HS), 4.53 (ddd, 2H, *J*=10.4, 9.3, 6.7 Hz, 2×C*H*N), 7.83 (t, 1H, *J*=7.7 Hz, H_4), 8.16 (d, 2H, *J*=7.7 Hz, H_4 and H_5). ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.4 and 19.7 (2×$(CH_3)_2CH$), 33.4 (2×*C*H$(CH_3)_2$), 34.1 (2×CH_2S), 84.0 (2×CHN), 122.7, 136.9, 150.6, 167.9 (S–C=N). IR (KBr): 2960, 2870, 1600 ($\nu_{S-C=N}$), 1450, 1360, 1310, 1020. Calcd for $C_{17}H_{23}N_3S_2$: C, 61.22; H, 6.95; N, 12.60. Found: C, 60.91; H, 6.92; N, 12.78.

3.5. Preparation of 8-quinolyl thiazolines 5

The 8-quinolyl thiazolines **5a**,**b**,**d**,**f** have been prepared using the general procedure described for the 2-quinolyl thiazolines **4**[3], in two steps, starting from dithioester **13**[8] and the corresponding aminoalcohol (*R*-2-aminobutanol, *S*-valinol, *S*-*tert*-leucinol and, respectively, *R*-phenylglycinol). They were purified by silica gel flash chromatography (pentane/diethyl ether: 70/30).

3.5.1. 8-[(*R*)-4,5-Dihydro-4-ethyl-2-thiazolyl]quinoline 5a. Viscous dark red oil, $[\alpha]_D^{20}=+138$ (*c* 1, acetone), overall yield=79%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.13 (t, 3H, *J*=7.3 Hz, C*H*$_3$CH$_2$), 1.74 (m, 1H, C*H*$_2$CH$_3$), 1.92 (m, 1H, C*H*$_2$CH$_3$), 3.07 (dd, 1H, *J*=10.8, 9.0 Hz, C*H*HS), 3.48 (dd, 1H, *J*=10.8, 8.5 Hz, CH*H*S), 4.56 (dt, 1H, *J*=8.5, 7.3 Hz, CHN), 7.31 (dd, 1H, *J*=8.3, 4.2 Hz, H_3), 7.57 (dd, 1H, *J*=8.1, 7.5 Hz, H_6), 7.77 (d, 1H, *J*=8.1 Hz, H_5), 8.04 (dd, 1H, *J*=8.3, 1.7 Hz, H_4), 8.25 (d, 1H, *J*=7.4 Hz, H_7), 8.90 (dd, 1H, *J*=4.2, 1.7 Hz, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 11.5 (*C*H$_3$CH$_2$), 28.4 (*C*H$_2$CH$_3$), 38.6 (CH_2S), 77.9 (CHN), 121.7, 126.4, 128.6, 130.8, 130.8, 133.0, 136.7, 145.9, 150.1, 165.5 (S–C=N). IR (KBr): 2960, 2920, 1650 ($\nu_{C=N}$), 1570, 1490, 1460, 1380, 1310, 1250. Calcd for $C_{14}H_{14}N_2S$: C, 69.39; H, 5.82; N, 11.56. Found: C, 69.93; H, 5.52; N, 11.17.

3.5.2. 8-[(*S*)-4,5-Dihydro-4-isopropyl-2-thiazolyl]quinoline 5b. Brown solid, mp 55 °C, $[\alpha]_D^{20}=-141$ (*c* 1, acetone), overall yield=81%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.15 (d, 6H, *J*=6.8 Hz, $CH(CH_3)_2$), 2.22 (sept, 1H, *J*=6.8 Hz, C*H*$(CH_3)_2$), 3.14 (t, 1H, *J*=10.7 Hz, C*H*HS), 4.43 (dd, 1H, *J*=10.7, 8.6 Hz, CH*H*S), 4.45 (ddd, 1H, *J*=10.4, 8.6, 6.8 Hz, CH=N), 7.46 (dd, 1H, *J*=8.3, 4.2 Hz, H_3), 7.60 (dd, 1H, *J*=8.1, 7.3 Hz, H_6), 7.92 (d, 1H, *J*=8.1, 1.4 Hz, H_5), 8.21 (dd, 1H, *J*=8.3, 1.8 Hz, H_4), 8.38 (dd, 1H, *J*=7.3, 1.4 Hz, H_7), 9.03 (dd, 1H, *J*=4.2, 1.8 Hz, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.4, 20.3 ($(CH_3)_2CH$), 33.6 (CH_2S), 36.3 (*C*H$(CH_3)_2$), 82.2 (CHN), 121.7, 126.5, 128.6, 130.7, 130.7, 133.2, 136.6, 146.0, 150.1, 165.5 (S–C=N). IR (KBr): 2970, 2850, 1610 ($\nu_{S-C=N}$), 1550, 1490, 1460, 1380, 1310, 1250. Calcd for $C_{15}H_{16}N_2S$: C, 70.27; H, 6.29; N, 10.93. Found: C, 70.32; H, 6.29; N, 11.12.

3.5.3. 8-[(*S*)-4,5-Dihydro-4-*tert*-butyl-2-thiazolyl]quinoline 5d. Brown solid, mp 75 °C, $[\alpha]_D^{20}=-157$ (*c* 1, acetone), overall yield=85%. ^{1}H NMR (400 M^{1}H NMR (400 MHz, $CDCl_3$): 1.12 (s, 9H, $(CH_3)_3C$), 3.11 (t, 1H, *J*=11.5 Hz, C*H*HS), 3.34 (dd, 1H, *J*=11.5, 8.7 Hz, CH*H*S), 4.34 (dd, 1H, *J*=11.5, 8.7 Hz, CHN), 7.43 (dd, 1H, *J*=8.3, 4.2 Hz, H_3), 7.57 (dd, 1H, *J*=8.1, 7.4 Hz, H_6), 7.89 (dd, 1H, *J*=8.1, 1.2 Hz, H_5), 8.16 (dd, 1H, *J*=8.3, 1.7 Hz, H_4), 8.38 (dd, 1H, *J*=7.4, 1.2 Hz, H_7), 8.99 (dd, 1H, *J*=4.2, 1.7 Hz, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 27.5 ($(CH_3)_3C$), 35.1 (CH_2S), 35.6 ($C(CH_3)_3$), 85.8 (CHN), 121.7, 126.5, 128.6, 130.8, 130.7, 133.2, 136.7, 146.0, 150.0, 165.2 (S–C=N). IR (KBr): 2970, 2850, 1610 ($\nu_{S-C=N}$), 1520, 1490, 1380, 1310, 1250. Mass *m*/*z*: 270 (M^+, 6), 213 (100), 155 (16), 128 (7), 101 (5), 59 (8). Calcd for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; N, 10.36; S, 11.86. Found: C, 70.76; H, 6.89; N, 10.10; S, 11.49.

3.5.4. 8-[(*R*)-4,5-Dihydro-4-phenyl-2-thiazolyl]quinoline 5f. Orange solid, mp 62 °C, $[\alpha]_D^{20}=-3.1$ (*c* 1, acetone), overall yield=82%. ^{1}H NMR (400 MHz, $CDCl_3$): 3.29 (t, 1H, *J*=10.9 Hz, C*H*HS), 3.81 (dd, 1H, *J*=10.9, 8.7 Hz, CH*H*S), 5.70 (dd, 1H, *J*=10.9, 8.7 Hz, CHN), 7.24–7.54 (m, 6H, H_3 and C_6H_5), 7.62 (dd, 1H, *J*=8.0, 7.4 Hz, H_6), 7.94 (dd, 1H, *J*=8.0, 1.3 Hz, H_5), 8.21 (dd, 1H, *J*=8.3, 1.7 Hz, H_4), 8.52 (dd, 1H, *J*=7.4, 1.3 Hz, H_7), 9.03 (dd, 1H, *J*=4.2, 1.7 Hz, H_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): 42.0 (CH_2S), 78.7 (CHN), 121.8, 126.5, 127.2, 127.8, 128.7, 129.0, 131.0, 131.1, 132.6, 136.8, 142.9, 145.9, 150.1, 167.6 (C=N). IR (KBr): 1650 ($\nu_{S-C=N}$), 1610, 1510, 1490, 1380, 1310, 1250. HRMS (MH^+) calcd for $C_{18}H_{15}N_2S$: 291.0956. Found: 291.0951. Calcd for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.86; N, 9.65; S, 11.04. Found: C, 73.73; H, 4.75; N, 9.60; S, 11.04.

3.6. Synthesis of (*S*)-(2-fluoro-phenyl)-4-isopropyl 4,5-dihydro-thiazole 8b

A mixture of dithioester **6**[8] (1.5 mmol) and *S*-valinol (1.5 mmol) was stirred at room temperature for 12 h. Then, the mixture was concentrated under reduced pressure, providing thioamide **7b** which was sufficiently pure according to ^{1}H NMR to be used without purification in the next step.

3.6.1. 2-Fluorobenzenethioamide 7b. Crude product: viscous green-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): 1.07 and 1.09 (2d, 6H, J=6.7 Hz, CH(CH_3)$_2$), 1.99 (s, 1H, OH), 2.17 (sept, 1H, J=6.7 Hz, CH(CH$_3$)$_2$), 3.87 (dd, 1H, J=11.1, 4.4 Hz, CHHOH), 3.94 (dd, 1H, J=11.1, 2.1 Hz, CHHOH), 4.76 (m, 1H, CHNH), 7.09 (ddd, 1H, J=11.8, 8.3, 1.2 Hz, H$_3$), 7.22 (dt, 1H, J=7.6, 1.2 Hz, H$_5$), 7.42 (m, 1H, H$_4$), 8.08 (dd, 1H, J=1.8 Hz, J=7.6 Hz, H$_6$), 8.11 (s, 1H, NH).

To crude **7b** diluted in 10 mL of THF, mesylchloride (2 mmol) was added. Then, NEt_3 (4 mmol) was added dropwise, at room temperature. Stirring was maintained for 10 min then water (10 mL) was added and the mixture extracted with dichloromethane (2×10 mL). The organic phase was dried ($MgSO_4$), solvents were evaporated and the residual oil was purified by flash chromatography on silica gel (pentane/diethyl ether: 80/20) to provide 2-fluorobenzene thiazoline **8b**.

Compound **8b**. Yellow oil, yield=78%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.05 and 1.13 (2d, 6H, J=6.7 Hz, CH(CH_3)$_2$), 2.14 (sept, 1H, J=6.7 Hz, CH(CH$_3$)$_2$), 3.17 (dd, 1H, J=10.9, 9.7 Hz, CHHS), 4.14 (dd, 1H, J=10.9, 9.1 Hz, CHHS), 4.83 (m, 1H, CHN), 7.11 (ddd, J=10.6, 8.1, 0.8 Hz, H^{arom}), 7.19 (dt, 1H, J=7.8, 0.8 Hz, H^{arom}), 7.42 (m, 1H, Ar–H^{arom}), 7.88 (dd, 1H, J=7.8, 1.7 Hz, H^{arom}). ^{19}F NMR (235.3 MHz, $CDCl_3$): −111.94 (m). ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.9 and 19.7 ((CH_3)$_2$CH), 33.1 ((CH$_3$)$_2$CH), 35.3 (d, J=3.3 Hz, CH_2S), 83.0 (CHN), 116.3 (d, J=22.0 Hz, C$_3$), 121.7 (d, J=11.4 Hz, C^{arom}), 124.0 (d, J=3.6 Hz, C^{arom}), 130.6 (d, J=2.5 Hz, C^{arom}), 132.1 (d, J=8.6 Hz, C^{arom}), 160.5 (d, J=254.5 Hz, FC^{arom}), 161.1 (d, J=4.9 Hz, S–C=N). IR (KBr): 2960, 2870, 1600 ($\nu_{S-C=N}$), 1590, 1480, 1450, 1380, 1270.

3.7. Synthesis of (*S*)-(2-diphenylphosphino-phenyl)-4-isopropyl 4,5-dihydro-thiazole 9b

A commercial 0.5 M solution of Ph_2PK in THF (1.1 mmol, 2.16 mL) was diluted with THF (4 mL) and refluxed under nitrogen. A solution of **8b** in 3 mL of THF was added dropwise and the mixture refluxed for 20 min. After cooling down to room temperature, hydrolysis with water and extraction with dichloromethane, the solution was dried with $MgSO_4$, filtered and evaporated. The product was purified by flash chromatography on silica gel with pentane, affording pure compound **9b**.

Yellow solid, mp 94 °C, $[\alpha]_D^{20}$=−42 (*c* 1, acetone), overall yield=82%. ^{1}H NMR (400 MHz, $CDCl_3$): 0.81 and 0.89 (2d, 6H, J=6.7 Hz, CH(CH_3)$_2$), 1.79 (oct, 1H, J=6.7 Hz, CH(CH$_3$)$_2$), 2.99 (t, 1H, J=10.6 Hz, CHHS), 3.27 (dd, 1H, J=10.6, 8.4 Hz, CHHS), 4.83 (ddd, 1H, J=10.6, 8.4, 6.8 Hz, CHN), 6.92 (ddd, 1H, J=3.8, 7.6, 1.2 Hz, H^{arom}), 7.19 (dt, 1H, J=7.6, 1.3 Hz, H^{arom}), 7.23–7.34 (m, 10H, H^{arom}), 7.39 (m, 1H, H^{arom}), 7.73 (ddd, 1H, J=7.8, 3.6, 1.3 Hz, H^{arom}). ^{31}P NMR (101.2 MHz, $CDCl_3$): −6.95. ^{13}C NMR (62.9 MHz, $CDCl_3$): 19.6 and 20.4 ((CH_3)$_2$CH), 33.6 ((CH$_3$)$_2$CH), 36.7 (CH_2S), 85.3 (CHN), 128.5 (d, J=1.9 Hz, C^{arom}), 128.63, 128.64, 128.68, 128.7, 130.2, 130.6 (d, J=3.1 Hz, C^{arom}), 134.2 (d, J=10.1 Hz, C^{arom}), 134.5 (d, J=10.7 Hz, C^{arom}), 134.9, 138.2 (d, J=20.1 Hz, C^{arom}), 138.3 (d, J=23.7 Hz, C^{arom}), 139.1 (d, J=24.5 Hz, C^{arom}), 139.2 (d, J=1.9 Hz, C^{arom}), 165.4 (S–C=N). IR (KBr): 3050, 2960, 2910, 2870, 1600 ($\nu_{S-C=N}$), 1550, 1460, 1430, 1380, 1360, 1260. Calcd for $C_{24}H_{24}NPS$: C, 74.01; H, 6.21; N, 3.60; S, 8.23. Found: C, 73.72; H, 6.32; N, 3.54; S, 7.78.

3.8. Synthesis of complex thia-1a/[Pd($C_3H_3Ph_2$)]$^+PF_6^-$

The same procedure as described in the literature for a bis(oxazolines) was used.[12] From [Pd(1,3-diphenylallyl)Cl]$_2$ (0.1 mmol), $AgPF_6$ (0.2 mmol) and thia-**1a** (0.2 mmol), the complex thia-**1a**/[Pd($C_3H_3Ph_2$)]$^+PF_6$ was obtained in 66% yield, as an orange solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ 0.89 (t, 6H, J=6.7, Hz, 2× CH_3CH$_2$), 1.56 (s, 6H, (CH_3)$_2$C), 2.13–2.42 (m, 4H, 2× CH$_3$CH_2), 3.14 (dd, 1H, J=6.3, 11.3, Hz, CHHS), 3.48 (dd, 1H, J=9.5, 11.3, Hz, CHHS), 4.84 (d, 1H, J=11.4 Hz, CH), 4.92 (m, 1H, NCH), 5.24 (d, 1H, J=11.4 Hz, CH), 6.35 (t, 1H, J=11.4 Hz, CH), 7.34–7.45 (m, 4H, H^{arom}), 7.63–7.73 (m, 6H, H^{arom}).

3.9. Synthesis of complex thia-2a/$PdCl_2$ and crystal structure determination

1.5 g of $(PdCl_2)_n$ were stirred with 40 mL of acetonitrile, at room temperature, for 24 h, under nitrogen. The orange solid was filtered, washed with diethyl ether and dried. Pd[Cl_2(CH_3CN)$_2$] was obtained as an orange solid in 91% yield (2 g). A mixture of Pd[Cl_2(CH_3CN)$_2$] (0.5 mmol) and ligand thia-**2a** (0.5 mmol) in dichloromethane (5 mL) was stirred at room temperature, for 24 h, under nitrogen. After evaporation of the solvent the crude thia-**2a**/$PdCl_2$, an orange solid, was characterized in ^{1}H NMR. Then, the complex was crystallized and one monocrystal was analysed by X-ray diffraction.

3.9.1. (*R*,*R*)-2,2′-Cyclohexylidene bis[4-ethyl-4,5-dihydrothiazoline]/$PdCl_2$ (thia-2a/$PdCl_2$). ^{1}H NMR (250 MHz, $CDCl_3$): 0.94 (t, 6H, J=7.4 Hz, 2×CH_3CH$_2$), 1.52–1.95 (m, 10H, (CH$_2$)$_5$), 2.15 (m, 2H, CH$_3$CHH), 2.45 (m, 2H, CH$_3$CHH), 3.22 (dd, 2H, J=11.4, 11.3 Hz, 2× CHHS), 3.35 (dd, 2H, J_1=11.3, 11.2 Hz, 2×CHHS), 4.95–5.20 (m, 2H, 2×CHN).

The crystal structure of thia-**2a**/$PdCl_2$ has been registered at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 236476.

$C_{16}H_{26}Cl_2N_2PdS_2$, Fw=487.81, orthorhombic, space group $P2_12_12_1$, a=10.361 (2) Å, b=13.425 (8) Å, c=14.655 (7) Å, V=2038.5(2) Å^{-3}. Z=4, D_x=1.589 Mg/m^3, λ(Mo Kα)=0.71073 Å, μ=13.77 cm^{-1}, F(000)=992, T=293 K. The sample (0.35×0.32×0.27 mm^3) was

studied on an automatic diffractometer CAD4 NONIUS with graphite monochromated Mo Kα radiation. The cell parameters are obtained by fitting a set of 25 high-theta reflections. The data collection ($2\theta_{max}=54°$, scan $\omega/2\theta=1$, $t_{max}=60$ s, range *HKL*: *h* 0,13; *k* −3,17; *l* −4,18) gives 4061 unique reflections from which 3110 with $I>2.0\sigma(I)$. After Lorenz and polarization corrections, the structure was solved with SIR-97, which reveals the non-hydrogen atoms of the compound. The whole structure was refined with SHELXL97 by the full-matrix least-square techniques (use of *F* square magnitude; *x*, *y*, *z*, β_{ij} for Pd, S, Cl, C and N atoms, *x*, *y*, *z* in riding mode for H atoms; 209 variables and 3110 observations; calcd $w=1/[\sigma^2(F_o^2)+(0.21P)^2]$ where $P=(F_o^2+2F_c^2)/3$ with the resulting $R=0.029$, $R_w=0.073$ and $S_w=01.127$ (residual $\Delta\rho\leq 0.67$ e Å^{-3}). The absolute configuration was unambiguously confirmed by the Flack parameter (0.02(4)).

3.10. Typical procedure for the Pd-catalysed allylic substitution

Under a nitrogen atmosphere, allylpalladium chloride dimer (0.012 mmol), the ligand (0.03 mmol) and solid potassium acetate (0.025 mmol) were mixed in 2 mL of dichloromethane for 30 min. Diphenylpropenyl acetate **10** (0.5 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (1.5 mmol) and the dimethyl malonate (1.5 mmol) were then successively added. The reaction mixture was stirred at 20 °C and monitored by TLC (pentane/diethyl ether: 80/20). The solvent was removed and the residue directly analysed by HPLC, using a Chiralpak AD analytical column Daicel (90/10 *n*-heptane/2-propanol, flow rate 1 mL/min, 252.1 nm). Conversions have been calculated from the integration of the corresponding peaks of **10** ($t=7.2$ min) and **11**. Enantiomeric excesses of (*E*)-methyl 2-methoxycarbonyl-3,5-diphenylpent-4-enoate **11** have been measured by HPLC; the separation of the two enantiomers was calibrated using racemic product: (*R*)-(+)-**11**, $t_1=$ 14.3 min; (*S*)-(−)-**11**, $t_2=20.1$ min).

Acknowledgements

The authors thank Pr. A. Pfaltz (University of Basel) for helpful information. Dr. L. Toupet (University of Rennes) is gratefully acknowledged for the X-ray crystal diffraction analysis. We also thank M. Lemarié for her precious assistance in HPLC analyses. This work has been performed within the 'PUNCHOrga' interregional network (Pôle Universitaire Normand de Chimie Organique). We gratefully acknowledge the 'Ministère de la Recherche et des Nouvelles Technologies', CNRS (Centre National de la Recherche Scientifique), the 'Région Basse-Normandie' and the European Union (FEDER funding) for financial support.

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