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Chiral oxazoline-1,3-dithianes: new effective nitrogen–sulfur donating ligands in asymmetric catalysis

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Abstract—A series of new chiral oxazoline-1,3-dithianes has been easily synthesized and used as ligands for asymmetric catalysis. The conjugate addition of Et_2Zn to enones resulted in ees of up to 69%, whereas the Pd-catalyzed allylic alkylation led to the expected products in almost quantitative yields and up to 90% enantioselectivity. The ligand's conformation has been explored using a combination of X-ray and NMR measurements, indicating the presence of a remarkable anomeric effect, which accounts for the preference of the oxazoline ring for the axial location.

1. Introduction

The development of new chiral ligands for metal-catalyzed asymmetric transformations is an important task in the field of enantioselective asymmetric synthesis.[1] The effect of sulfur chelation on the level of asymmetric induction for bidentate ligands and catalysts has been widely reported. An inherent characteristic of thioether ligands is that upon coordination with the metal, the sulfur atom becomes stereogenic[2] and the close proximity of the chirality to the coordination sphere of the transition metal may be beneficial. Moreover, in combination with N chelation sites, thioether ligands have been successfully tested and a number of asymmetric catalytic C–C bond forming reactions relying to Pd-catalyzed allylic substitutions,[3] to additions to aldehydes[4] and to conjugate additions,[5] have been reported so far.

However, whereas the mono[3c,e,6] and also to some extent the *S*,*S*-dithioeter moiety[7] have been used to date, the 1,3-dithianyl motif appears unprecedented in the design and synthesis of new hybrid ligands for asymmetric catalysis.

Herein, we report a simple, modular and efficient design of enantiomerically pure chiral oxazoline-1,3-dithianes, which when associated with a positional scanning like strategy allows the synthesis of a new type of ligands and a quick optimization of their structure.

2. Result and discussion

2.1. Ligand synthesis

In all cases, homochiral oxazoline-1,3-dithianes were prepared by cyclic dehydration of the intermediate hydroxyamides. These were accessed by treating the readily available 1,3-dithiane-2-carboxylic acid **1** and 2-methyl-1,3-dithiane-2-carboxylic acid **2** with enantiomerically pure 2-amino alcohols from the chiral pool in the presence of DCC in CH_2Cl_2 as the solvent. Conversion of the hydroxyl group into a good nucleofuge[8] followed by cyclization was performed through tosylation in the presence of DMAP and Et_3N to give ligands **7**–**10**. In the case of 1,2-disubstituted 2-amino alcohols, oxazoline formation according to this procedure being unsuccessful, the modified protocol by Vorbrüggen was applied.[9] In this procedure, the acid and the 2-amino alcohols, (1*R*,2*S*)-norephedrine and (1*S*,2*R*)-2-amino-1,2-diphenylethanol, were treated with hexachloroethane/PPh_3 and a base to generate oxazolines (*S*,*S*)-**11** and (*R*,*R*)-**12**, respectively, in a single step without isolation of the intermediate hydroxyamide (Scheme 1).

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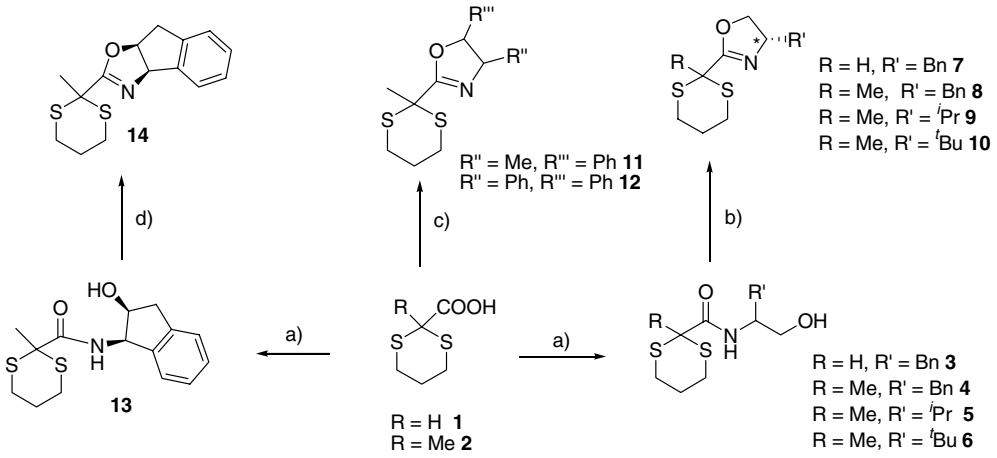
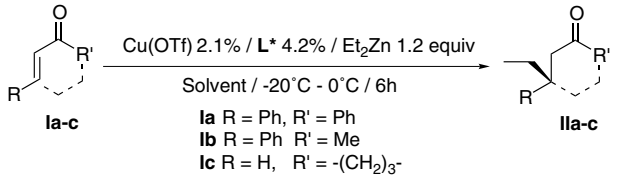


Scheme 1. Reagents and conditions: (a) amino alcohol, DCC, CH_2Cl_2, 18 h, rt; (b) TsCl, DMAP, Et_3N, CH_2Cl_2, 6 h, rt; (c) PPh_3, Cl_3CCCl_3, Et_3N, CH_3CN, CH_2Cl_2, 10 h, rt; (d) $Zn(OAc)_2$, 170 °C, 8 h.

Finally, starting from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, a synthetic route to **14** was envisaged among those reported in the literature,[10] in which cyclization of the intermediate carboxyamide **13** promoted by Zn acetate occurred with full retention of configuration and complete stereochemical integrity of the carbon–oxygen bond at C-5, thus giving rise to the *cis*-oxazoline system in good yields.



Scheme 2.

2.2. Conjugate addition

The new ligands were used in the copper-catalyzed conjugated addition of diethylzinc to enones. The asymmetric formation of carbon–carbon bonds using the asymmetric conjugate addition reaction has been widely investigated. Conditions have been developed, using a catalytic quantity of copper triflate and chiral ligands associated to an organozinc reagent to perform this reaction in high yield and good to excellent enantioselectivity. In particular, chiral phosphonites,[11] phosphoramidites[12] and other chiral P, N ligands[13] have been used. However, an important limitation is that they often exhibit high substrate specificity. Further efforts are therefore required to design new chiral catalysts, which can be applied more generally to different cyclic and acyclic substrates. Despite the early results obtained with thiolate ligands in the asymmetric copper catalyzed conjugate addition to enones,[5a,14] sulfur ligands have been less studied than their phosphorus counterparts. With a new set of chiral ligands in hand, we first evaluated their performance in the reaction of diethylzinc with a representative acyclic enone, chalcone **Ia**. The catalytic system was generated in situ by the addition of a twofold excess of the corresponding ligand to a solution of copper salts followed by the addition of diethylzinc. Reactions were carried out in either toluene or diethyl ether at −20 °C giving in all cases as the sole product, the 1,4 adduct in satisfactory yields (Scheme 2).

Different copper(I) or copper(II) salts could be used as precursors of the active copper(I) catalyst, but only triflates and in particular the CuOTf-based catalysts gave higher conversions. Diethyl ether and toluene were suitable solvents, the former however leading to better enantioselectivity.

For all the additions, the product was obtained in good yields. The presence of a methyl group on the dithianyl ring had a fundamental influence, since the reaction performed using **7** led (Table 1, entry 1) only to decomposition of the ligand with no trace of the addition product being recovered from the reaction mixture. Substituents in close proximity to the oxazoline nitrogen were found to exert a strong influence on the stereochemical outcome. A significant improvement in the enantioselectivity (62% ee) with respect to the 15% ee obtained in the case of compound **11** (entry 8) was achieved (entry 2) by using ligand **8**, in which instead of a methyl group, a benzyl group lies adjacent to the nitrogen. This trend also suggests that even bulkier substituents, such as phenyl next to the oxygen, might exert only a negligible influence. A further improvement in enantioselectivity (69% ee) was obtained (entry 9) in the case of ligand **14** derived from the amino indanol in which a significant steric hindrance at the α-position to nitrogen combines with the formation of a tricyclic rigid motif. Strangely enough, ligand **9** with a branched group such as the isopropyl group in proximity to the oxazoline nitrogen did not prove beneficial regarding the enantioselectivity (entry 5). We then examined the behaviour of other Michael acceptors, benzalacetone **Ib** and 2-cyclohexene-1-one **Ic**, under the optimized experimental conditions previously used for chalcone using ligands **8**, **9** and **14**. In the literature, catalytic conjugate additions of organometallic reagents with chiral ligand/metal complexes are reported to show enantioselectivity for only one spe-

Table 1. Cu/L* catalyzed enantioselective 1,4-conjugate addition of Et_2Zn to enones[a]

Entry	L*	Enone	Adduct	Solvent	Yield (%)[b]	ee (%)[c]	Config.
1	(*S*)-**7**	**Ia**	**IIa**	Toluene	—	—	—
2	(*S*)-**8**	**Ia**	**IIa**	Et_2O	80	62	*S*
3	(*S*)-**8**	**Ib**	**IIb**	Toluene	55	46	*S*
4	(*S*)-**8**	**Ic**	**IIc**	Toluene	>95	37	*S*
5	(*S*)-**9**	**Ia**	**IIa**	Et_2O	73	50	*S*
6	(*S*)-**9**	**Ib**	**IIb**	Toluene	49	36	*S*
7	(*S*)-**9**	**Ic**	**IIc**	Toluene	>95	24	*S*
8	(*S*,*S*)-**11**	**Ia**	**IIa**	Et_2O	60	15	*R*
9	(*R*,*S*)-**14**	**Ia**	**IIa**	Et_2O	77	69	*R*
10	(*R*,*S*)-**14**	**Ib**	**IIb**	Toluene	54	53	*R*
11	(*R*,*S*)-**14**	**Ic**	**IIc**	Toluene	>95	51	*R*

[a] Reaction conditions as in Scheme 2.
[b] Yields of isolated products.
[c] For ee determination see Section 4.

cific type of enone. So far, Ni^{II}/chiral amino alcohol complexes are enantioselective for the addition of Et_2Zn to acyclic enones, but for cyclic enones no enantioselectivity was found.[15] Conversely, the application to this reaction of chiral phosphorus ligands derived from taddol afforded poor enantioselectivities for acyclic enones, the best results being obtained with chalcone.[16] A substantial improvement was achieved by Feringa,[17] who obtained relatively high ee values for both cyclic and acyclic enones by using phosphorus amidites. The trend, which emerges from Table 1 indicates that both acyclic enones **Ib** and **c** afford moderate to very good yields of the expected adducts though with lower but still significant enantioselectivities as compared to chalcone. It should be pointed out that again ligand **14** gave the best enantioselectivities for all the investigated enones affording 53% ee for the *trans*-4-phenyl-3-buten-2-one and 51% ee for the 2-cycloexen-1-one.

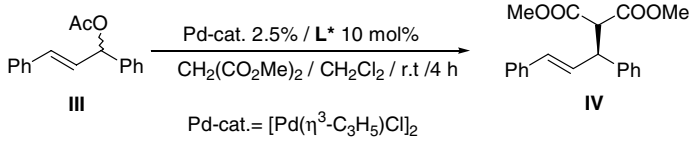
Regarding the nature of the catalytic species in the conjugate addition, an ML_2-type complex was formed using both a 1:1 or a 1:2 ligand/metal ratio. This result is supported experimentally by the ESI mass spectrum of the Cu^{2+}/ligand complex. The observed ESI-MASS molecular peak of 649, indicates that four of the eight ligand sites, and most likely one of the thienyl sulfur atom and the nitrogen of each oxazoline ring, are bound to the copper. The two OTf counterions are outside the tetrahedral coordination sphere, and therefore the 1,3-dithianyl oxazoline behaves as a bidentate ligand.

2.3. Pd-catalyzed allylic substitution

Pd-catalyzed allylic substitution reactions have been intensively studied with sulfur containing ligands over the past few years. Williams[18] prepared various *S*,*N* ligands containing oxazoline functionalities and sulfur as an auxiliary donor atom providing enantioselectivities of 40–96%. The idea of using ligands containing two different donor atoms has been exploited for palladium catalyzed allylic substitution, wherein it is anticipated[19] that the differing electronic behaviour of the two donor atoms will be relayed to the intermediate palladium allyl complex and thereby import asymmetric induction. The synthesized ligands **7**–**12** and **14** were tested in this catalytic system to see if they were able to bind to a suitable palladium precursor and interact with the allylic substrate. Allylic substitutions of acetate were carried out using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and a mixture of dimethyl malonate, *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride at room temperature (Scheme 3). The ligand and palladium pre-catalysts were premixed in CH_2Cl_2 at room temperature for 1 h prior to the reaction. After 4 h, the isolated product **IV** was assayed for enantiomeric excess by employing HPLC analysis on a Daicel Chiralcel AD-H column with absolute configuration determined by comparison with literature values.[20]

The results for the Pd-catalyzed allylic substitution are reported in Table 2. The presence of a methyl substituent on the dithianyl ring had no influence on the reaction outcome (compare entries 1 and 2) with both ligands **7** and **8** providing the desired product in almost quantitative yields and moderate enantioselectivity.

A significant improvement in the enantioselectivity materialized with ligand **9**, whereas the highest level of enantioselectivity (90% ee) was achieved with ligand **10** (entry 4). This confirms that superior levels of asymmetric induction can be rationalized in terms of steric factors. The same trend emerges when considering disubstituted ligands **11**, **12** and **14**. Significant improvements of the enantioselectivity with respect to ligand **11**



Scheme 3.

Table 2. Allylic substitution of ***rac*-III** in the presence of oxazoline-dithianyl ligands[a]

Entry	L*	Yield (%)[b]	ee (%)[c]	Config.
1	(*S*)-**7**	94	50	*S*
2	(*S*)-**8**	96	54	*S*
3	(*S*)-**9**	96	62	*S*
4	(*S*)-**10**	96	90	*S*
5	(*S*,*S*)-**11**	98	48	*S*
6	(*R*,*R*)-**12**	98	74	*R*
7	(*R*,*S*)-**14**	94	72	*R*

[a] Reaction conditions as in Scheme 3.
[b] Yields of isolated products.
[c] For ee determination see Section 4.

(ee 48%) were obtained using ligand **12** (ee 74%) containing a phenyl group instead of a methyl group, while ligand **14** provided good enantioselectivity (72% ee) confirming that hindered substituents on the oxazoline ring were influential to ensure different enantiodiscrimination. The configuration of the final product was (*S*) using ligand (*S*,*S*)-**11** (entry 5) and (*R*) using (*R*,*R*)-**12** (entry 6).

Having examined the effect of the oxazoline ring substituents on the stereochemical outcome of the two prototypical reactions studied, and in an attempt to further improve the enantioselectivity we turned our attention to the effect of placing substituents on the thianyl ring. For this, we synthesized the two 4,6-dimethyl-1,3-dithianyl oxazolines **19a** and **19b**. The target ligands were obtained following the sequence reported in Scheme 4. Separation of the diastereomeric mixture of the hydroxyamides followed by ring closure afforded the stereochemically pure ligands, which were fully characterized. However, serious difficulties encountered in their crystallization hindered the establishment of their absolute configuration.

Though not configurationally defined, these ligands modified in the 1,3-dithianyl ring were engaged in the conjugate addition and allylic alkylation under the optimized reaction conditions previously found. The following features emerged when their reaction outcome was compared to that obtained using ligand (*S*)-**8** bearing the same substituent in the oxazoline ring (Table 3).

Whereas ligand **19a** had an effect on the enantioselective conjugate addition (ee increased) but was detrimental for the allylic alkylation (ee decreased) (entry 2), the opposite trend was observed on using ligand **19b** (entry 3). However, both displayed marginal effects with

Table 3. Effect of the substitution on the 1,3-dithianyl ring on the catalytic efficiency

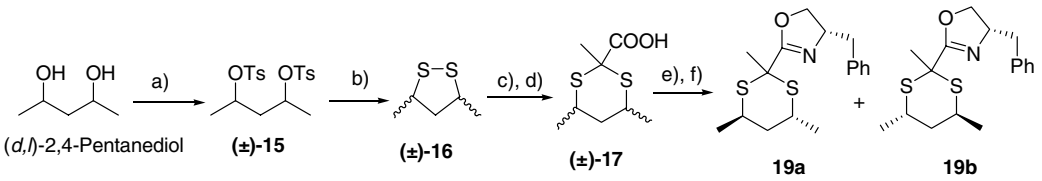
Entry	L*[a]	Conjugate addition	Allylic substitution
1	(*S*)-**8**	Yield: 80% ee 62% (*S*)	Yield: 94% ee 54% (*S*)
2	**19a**	Yield: 45% ee 70% (*S*)	Yield: 98% ee 48% (*S*)
3	**19b**	Yield: 50% ee 44% (*S*)	Yield: 98% ee 66% (*S*)

[a] For the description of **19a** and **19b** see Section 4.

respect to the reference compound (*S*)-**8** (entry 1) and for this reason they were not subjected to further investigations nor further efforts were made in order to establish their absolute stereochemistry.

2.4. Ligand conformational considerations

In order to understand these results better, it was essential to shed some light on the ligand structure. The conformational analysis of several 2-substituted-1,3-dithianes has been reviewed[21] and the energy differences between axially and equatorially substituted structures have been evaluated in terms of anomeric effect (ΔE). In general, for substituted heterocyclic systems, the axial conformer is favoured when electronic delocalization is dominant and the equatorial position is preferred when steric effects predominate. According to the interpretation of the anomeric effect given by Edward,[22] electrostatic dipole/dipole repulsions should disfavour the equatorial conformer, while dipole–dipole attraction should favour the axial one. Juaristi studied the conformational equilibria of 2-substituted-1,3-dithianes, which show[23] the expected interplay of steric, electrostatic and stereoelectronic interactions. The low temperature (−90 to −100 °C) ^{13}C NMR spectra of mobile dithianes give rise to two sets of signals, which correspond to the axial and equatorial conformers and integration of the peak areas afforded the equilibrium constants and the conformational free energy differences. On the other hand, in the low temperature (−90 to −100 °C) ^{13}C NMR spectra of 2-carboxylic-1,3-dithiane, no signals for the equatorial conformer were detected.[24] In order to establish the preferred conformation of the synthesized oxazoline 1,3-dithianes, a ^{1}H NMR analysis was carried choosing **14** as a representative ligand. In C_6D_6, in the temperature range from −85 to +20 °C, the spectra showed the existence of a single isomer in solution. To establish if the oxazoline ring occupied the equatorial (a) or axial (b) position, a single crystal X-ray analysis[25] was performed on **14**, which clearly showed that the oxazoline ring occupies the axial position, thus confirming the presence of a significant anomeric effect and the prevalence of the electronic over the steric effects (Fig. 1).



Scheme 4. Reagents and conditions: (a) TsCl, Pyridine, 0 °C, 40 h. (b) Na_2S, S_8, DMF, 85 °C, 72 h. (c) $LiAlH_4$, THF, 3 h, 60 °C. (d) pyruvic acid, benzene, *p*-TsOH, 80 °C, 3 h. (e) phenylalaninol, DCC, CH_2Cl_2, 18 h, rt. Separation of the two diastereoisomers by column chromatography. (f) TsCl, DMAP, Et_3N, CH_2Cl_2, 6 h, rt.

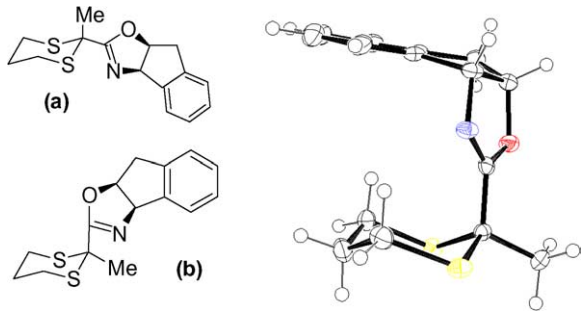


Figure 1. ORTEP drawing of **14**.

3. Conclusions

The design and synthesis of a new class of chiral oxazoline 1,3-dithianes has been achieved and their efficiency as ligands in both copper-catalyzed diethylzinc addition to enones and palladium-catalyzed allylic substitution investigated. Though there are not unifying views on the ligand structure–enantioselectivity relationship as yet, in both these reactions the asymmetric induction appears closely related to the steric hindrance exerted by the group adjacent to the oxazoline nitrogen. The potential of the reported ligands in other catalytic asymmetric transformations is currently under investigation in our laboratory.

4. Experimental

4.1. General remarks

Melting points (uncorrected) were determined with a Büchi melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ solutions or C_6D_6 as the solvent at 300 and 400 MHz and 75 and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million relative to $CHCl_3$ ($\delta = 7.26$ for ^{1}H and $\delta = 77.0$ for ^{13}C). J values are given in hertz. ^{13}C NMR spectral assignments were made by DEPT experiments. IR spectra were recorded on a Perkin–Elmer model 257 grating spectrometer. Mass spectra were obtained using a VG 7070-E spectrometer at an ionizing voltage of 70 eV or with an electronspray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent. $[\alpha]_D^{20}$ values were determined with Perkin–Elmer Polarimeter 341. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar atmosphere. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Et_2O was distilled from phosphorus pentoxide twice. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with bp 40–60 °C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Preparative thick layer chromatography was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified by conventional methods if needed.

4.2. General procedures for the synthesis of the carboxylic acid

To a solution of the appropriate thiane (33.3 mmol) in 167 mL of anhydrous THF, *n*-BuLi (solution 1.6 M in hexane, 34.9 mmol) was added at −20 °C. After 1.5 h at −20 °C, CO_2 (dry ice) was added quickly (166.3 mmol) and the mixture was stirred for 1 h and at room temperature for 2 h. After quenching with NH_4Cl, the mixture was concentrated to reduce the volume of the solvent. The aqueous layer was acidified to pH 3 with HCl 1 M, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. The crude was purified on column chromatography (petroleum ether/EtOAc 4:1) to afford the corresponding products **1** and **2**.

4.2.1. 1,3-Dithiane-2-carboxylic acid 1. Yield: 45%. Mp 114–116 °C. ^{1}H NMR (300 MHz, CD_3OD) δ: 1.84–1.98 (2H, m), 2.48–2.55 (2H, m), 3.15–3.24 (2H, m), 4.14 (1H, s), 4.80 (1H, br s) ppm. ^{13}C NMR (75.3 MHz, CD_3OD) δ: 25.18 (CH_2), 26.07 ($2CH_2$), 41.08 (CH), 172.17 (C=O) ppm. EI-MS (m/z): 164 (M^+).

4.2.2. 2-Methyl-1,3-dithiane-2-carboxylic acid 2. Yield: 70%. Mp 137.9–140.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.55 (3H, s), 1.63–1.79 (1H, m), 2.01–2.12 (1H, m), 2.48–2.56 (2H, m), 3.25–3.36 (2H, m), 10.13 (1H, br s) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 23.91 (CH_3), 25.40 (CH_2), 28.08 ($2CH_2$), 45.63 (C), 178.06 (C=O) ppm. EI-MS (m/z): 178 (M^+).

4.3. General procedures for the synthesis of amides 3–6

To a solution of the carboxylic acid (3.04 mmol) in 18 mL of CH_2Cl_2, DCC (3.19 mmol) was added in small portions at 0 °C. After 30 min at 0 °C, the amino alcohol (2.9 mmol) was added and the mixture stirred at room temperature for 18 h. After filtering on Celite, the solution was washed with 10% Na_2CO_3 and brine. The organic phases were dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc 1:1) to afford amides **3**–**6**.

4.3.1. *N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-1,3-dithiane-2-carboxamide 3. Yield: 40%. $[\alpha]_D = -29.2$ (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.81–1.92 (2H, m), 2.43–2.55 (2H, m), 2.65–2.87 (4H, m), 3.48–3.64 (2H, m), 4.08–4.14 (1H, m), 4.19 (1H, s), 6.69 (1H, br d, $J = 7.59$ Hz), 7.04–7.22 (5H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 25.22 (CH_2), 27.82 ($2CH_2$), 37.01 (CH_2), 46.30 (CH), 53.67 (CH), 63.87 (CH_2), 126.72 (ArCH), 128.75 (2ArCH), 129.54 (2ArCH), 137.82 (ArC), 168.85 (C=O) ppm. EI-MS (m/z): 297 (M^+).

4.3.2. *N*-[(1*S*)-1-Benzyl-2-hydroxyethyl]-2-methyl-1,3-dithiane-2-carboxamide 4. Yield: 53%. $[\alpha]_D = -17.8$ (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (3H, s), 1.66–1.91 (2H, m), 2.36–2.41 (2H, m), 2.44–2.61 (2H, m), 2.64–2.95 (2H, m), 3.50–3.75 (2H, m), 4.16

(1H, m), 7.10–7.24 (5H, m) 7.36 (1H, br d) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 24.2 (CH_2), 28.3 (CH_3), 29.5 ($2CH_2$), 37.1 (CH_2), 53.4 (CH), 56.1 (C), 64.0 (CH_2), 126.1 (ArCH), 128.3 (2ArCH), 129.5 (2ArCH), 138.2 (ArC), 172.6 (C=O) ppm. EI-MS (*m*/*z*): 311 (M^+).

4.3.3. *N*-[(1*S*)-1-(Hydroxymethyl)-2-methylpropyl]-2-methyl-1,3-dithiane-2-carboxamide 5. Yield: 43%. $[\alpha]_D = -18.6$ (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86–0.94 (6H, m), 1.62 (3H, s), 1.73–1.92 (2H, m), 1.99–2.07 (1H, m), 2.63–2.70 (2H, m), 2.83–2.96 (2H, m), 3.20–3.26 (1H, m), 3.56–3.70 (3H, m), 7.45 (1H, br d, $J = 8.9$ Hz) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 18.85 (CH_3), 20.04 (CH_3), 24.33 (CH_2), 28.14 (CH_3), 28.98 ($2CH_2$), 29.13 (CH), 55.56 (C), 58.16 (CH), 63.70 (CH_2), 171.73 (C=O) ppm. EI-MS (*m*/*z*): 263 (M^+).

4.3.4. *N*-[(1*S*)-1-(Hydroxymethyl)-2,2-dimethylpropyl]-2-methyl-1,3-dithiane-2-carboxamide 6. Yield: 41%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 (9H, s), 1.72 (3H, s), 1.79–1.95 (1H, m), 2.03–2.16 (1H, m), 2.38 (br s, 1H), 2.69–2.78 (2H, m), 2.91–3.06 (2H, m), 3.51–3.57 (1H, m), 3.77–3.84 (1H, m), 3.95 (1H, dd, $J = 3.6$ Hz, $J = 11.1$ Hz), 7.55 (1H, br d, $J = 9.1$ Hz) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 25.32 (CH_2), 27.32 ($3CH_3$), 29.73 (CH_3), 34.29 ($2CH_2$), 56.44 (C), 61.54 (CH), 63.98 (CH_2), 172.30 (C=O) ppm. EI-MS (*m*/*z*): 277 (M^+).

4.4. General procedures for the synthesis of oxazoles 7–10

To a solution of the amide (1.2 mmol) in 8.5 mL of CH_2Cl_2 were added TsCl (1.8 mmol), Et_3N (3.6 mmol) and DMAP (0.06 mmol). After 18 h at room temperature, a solution of Na_2CO_3 10% was added and the mixture stirred for 20 min. The solution was extracted with CH_2Cl_2 (3×30 mL). The organic phases were dried over $MgSO_4$, filtered and concentrated. The crude was purified on column chromatography on silica gel (petroleum ether/EtOAc 3:1) to afford oxazoles **7**–**10**.

4.4.1. (4*S*)-4-Benzyl-2-(1,3-dithian-2-yl)-4,5-dihydro-1,3-oxazole 7. Yield: 73%. Mp 81.3–83.2 °C $[\alpha]_D = -19$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26–1.38 (2H, m), 1.83–1.95 (2H, m), 2.15 (1H, dd, $J = 7.7$ Hz, $J = 13.7$ Hz), 2.57 (1H, dd, $J = 5.9$ Hz, $J = 13.7$ Hz), 2.76–2.86 (2H, m), 3.29–3.44 (2H, m), 3.80–3.90 (1H, m), 4.11 (1H, s), 6.61–6.81 (5H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 25.41 (CH_2), 27.08 ($2CH_2$), 37.85 (CH), 41.44 (CH_2), 67.75 (CH), 71.81 (CH_2), 126.36 (ArCH), 128.71 (2ArCH), 129.69 (2ArCH), 138.31 (ArC), 165.82 (C=N) ppm. EI-MS (*m*/*z*): 279 (M^+). $C_{14}H_{17}NOS_2$: C, 60.18; H, 6.13; N, 5.01. Found: C, 60.13; H, 6.10; N, 5.03.

4.4.2. (4*S*)-4-Benzyl-2-(2-methyl-1,3-dithian-2-yl)-4,5-dihydro-1,3-oxazole 8. Yield: 90%. Mp 38.4–39.6 °C $[\alpha]_D = -28$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43–1.51 (2H, m), 1.71 (3H, s), 2.04–2.15 (2H, m), 2.30 (1H, dd, $J = 7.7$ Hz, $J = 13.8$ Hz), 2.69 (1H, dd, $J = 5.9$ Hz, $J = 13.8$ Hz), 3.21–3.30 (2H, m), 3.44–3.60 (2H, m), 3.92–4.03 (1H, m), 6.84–7.00 (5H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 24.78 (CH_2), 26.75 (CH_3), 28.38 ($2CH_2$), 41.78 (CH_2), 43.09 (C), 67.27 (CH), 71.84 (CH_2), 126.40 (ArCH), 128.40 (2ArCH), 129.44 (2ArCH), 138.18 (ArC), 168.90 (C=N) ppm. EI-MS (*m*/*z*): 293 (M^+). $C_{15}H_{19}NOS_2$: C, 61.39; H, 6.53; N, 4.77. Found: C, 61.37; H, 6.50; N, 4.79.

4.4.3. (4*S*)-4-Isopropyl-2-(2-methyl-1,3-dithiane-2-yl)-4,5-dihydro-1,3-oxazole 9. Yield: 81%. $[\alpha]_D = -64$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.70 (3H, m), 0.79 (3H, m), 1.53 (3H, m), 1.55–1.74 (2H, m), 1.91–1.98 (1H, m), 2.45 (2H, d, $J = 12.89$ Hz), 3.04–3.16 (1H, m), 3.25–3.38 (1H, m), 3.71–3.93 (2H, m), 4.06–4.16 (1H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 18.22 (CH_3), 18.57 (CH_3), 24.70 (CH_2), 26.79 (CH_3), 28.18 ($2CH_2$), 33.06 (CH), 42.81 (C), 70.33 (CH_2), 72.08 (CH), 168.57 (C=N) ppm. EI-MS (*m*/*z*): 245 (M^+). $C_{11}H_{19}NOS_2$: C, 53.84; H, 7.80; N, 5.71. Found: C, 53.81; H, 7.82; N, 5.70.

4.4.4. (4*S*)-4-*tert*-Butyl-2-(2-methyl-1,3-dithiane-2-yl)-4,5-dihydro-1,3-oxazole 10. Yield: 60%. $[\alpha]_D = -68$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.97 (9H, s), 1.75 (3H, s), 1.81–1.92 (1H, m), 2.12–2.20 (1H, m), 2.61–2.75 (2H, m), 3.25–3.39 (1H, m), 3.42–3.59 (1H, m), 3.86–3.99 (1H, m), 4.18–4.35 (2H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 24.60 (CH_2), 26.15 ($3CH_3$), 27.06 (CH_3), 28.42 (CH_2), 28.51 (CH_2), 34.08 (C), 69.51 (CH_2), 75.74 (CH), 167.08 (C=N) ppm. EI-MS (*m*/*z*): 259 (M^+). $C_{11}H_{21}NOS_2$: C, 55.56; H, 8.16; N, 5.40. Found: C, 55.53; H, 8.15; N, 5.42.

4.5. General procedures for the synthesis of oxazoles 11–12

To a stirred suspension of 0.18 g (1 mmol) of the carboxylic acid **2** in 3.3 mL of dry CH_3CN were added amino alcohol (1 mmol), triphenylphosphine (0.66 g, 2.5 mmol) and triethylamine (0.7 mL). The mixture was cooled to 0 °C and then a solution of 0.52 g (2.2 mmol) of hexachloroethane in 2 mL of CH_2Cl_2 was added slowly. After 18 h at room temperature, water was added, the mixture extracted with EtOAc (3×15 mL), dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc 5:1) to afford the oxazoles **11** and **12**.

4.5.1. (4*S*,5*S*)-4-Methyl-2-(2-methyl-1,3-dithian-2-yl)-5-phenyl-4,5-dihydro-1,3-oxazole 11. Yield: 78%. $[\alpha]_D = +40$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.02 (3H, d, $J = 6.76$ Hz), 1.29–1.53 (2H, m), 1.86 (3H, s), 1.99–2.10 (2H, m), 3.23–3.41 (2H, m), 3.72–3.84 (1H, m), 4.55 (1H, d, $J = 7.6$ Hz), 6.90–7.12 (5H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 21.29 (CH_2), 24.42 (CH_3), 26.92 ($2CH_2$), 28.19 (CH_3), 42.70 (C), 70.89 (CH), 88.24 (CH), 125.55 (2ArCH), 128.14 (2ArCH), 128.88 (ArCH), 141.57 (ArC), 167.96 (C=N) ppm. EI-MS (*m*/*z*): 293 (M^+). $C_{15}H_{19}NOS_2$: C, 61.39; H, 6.53; N, 4.77. Found: C, 61.37; H, 6.50; N, 4.75.

4.5.2. (4*R*,5*R*)-4-Methyl-2-(2-methyl-1,3-dithian-2-yl)-4,5-diphenyl-4,5-dihydro-1,3-oxazole 12. Yield: 72%. Mp 102.5–103.1 °C. $[\alpha]_D = +77$ (*c* 0.3, $CHCl_3$). ^{1}H

NMR (300 MHz, $CDCl_3$) δ: 1.29–1.49 (2H, m), 1.90 (3H, s), 1.99–2.08 (2H, m), 3.26–3.43 (2H, m), 4.92 (1H, d, $J = 7.15$ Hz), 5.01 (1H, d, $J = 7.15$ Hz), 6.87–7.10 (10H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 24.41 (CH_2), 26.97 (CH_3), 28.17 (CH_2), 28.31 (CH_2), 42.50 (C), 78.76 (CH), 89.27 (CH), 125.78–129.19 (10ArCH), 141.47 (ArC), 142.82 (ArC), 169.98 (C=N) ppm. EI-MS (m/z): 355 (M^+). $C_{20}H_{21}NOS_2$: C, 67.57; H, 5.95; N, 3.94. Found: C, 67.59; H, 5.93; N, 3.92.

4.5.3. *N*-[(1*R*,2*S*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl]-2-methyl-1,3-dithiane-2-carboxamide 13. To a solution of carboxylic acid **2** (0.30 g, 1.68 mmol) in 10 mL of CH_2Cl_2, DCC (0.35 g, 1.68 mmol) was added in small portions at 0 °C. After 30 min at 0 °C, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol (0.24 g, 1.60 mmol) was added and the mixture stirred at room temperature for 18 h. After filtering on Celite, the solution was washed with 10% Na_2CO_3 and brine. The organic phases were dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel chromatography (petroleum ether/EtOAc 3:1) to afford 0.28 g (58%) of the amide. $[\alpha]_D = +17.6$ (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.77 (3H, s), 1.83–1.94 (1H, m), 2.08–2.19 (2H, m), 2.70–2.77 (2H, m), 2.94–3.13 (2H, m), 3.22 (1H, dd, $J = 5.64$ Hz, $J = 16.22$ Hz), 4.68–4.73 (1H, m), 5.35 (1H, dd, $J = 6.48$ Hz, $J = 9.08$ Hz), 7.25–7.30 (4H, m), 7.84 (1H, br d, $J = 9.5$ Hz) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 24.38 (CH_2), 28.16 (CH_3), 29.08 (CH_2), 29.11 (CH_2), 40.10 (CH_2), 55.07 (C), 58.73 (CH), 74.02 (CH), 124.78 (ArCH), 125.73 (ArCH), 127.63 (ArCH), 128.73 (ArCH), 140.19 (ArC), 140.55 (ArC), 171.85 (C=O) ppm. EI-MS (m/z): 309 (M^+).

4.5.4. (3a*R*,8a*S*)-2-(2-Methyl-1,3-dithian-2-yl)-8,8a-dihydro-3a*H*-indeno-[1,2-*d*]-[1,3]-oxazole 14. $Zn(OAc)_2$ (2.34 g, 12.9 mmol) previously dried at 160 °C for 3 h at 10^{-1} mmHg and amide **13** (0.4 g, 1.3 mmol) were stirred at 170 °C for 8 h. Water was added and the mixture extracted with EtOAc (3×20 mL), dried over $MgSO_4$, filtered and concentrated. The crude was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:1) to afford **(14)** (0.17 g, 45%). Mp 91.5–92.1 °C. $[\alpha]_D = +175$ (c 0.3, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6) δ: 1.42–1.56 (2H, m), 1.80 (3H, s), 1.99–2.06 (1H, m), 2.17–2.20 (1H, m), 2.79 (1H, dd, $J = 5.18$ Hz, $J = 17.29$ Hz), 2.99–3.11 (2H, m), 3.50–3.59 (1H, m), 4.58 (1H, dd, $J = 6.91$ Hz, $J = 15.56$ Hz), 5.21 (1H, d, $J = 8.64$ Hz), 6.88–7.01 (3H, m), 7.43 (1H, br d, $J = 7.22$ Hz) ppm. ^{13}C NMR (75.3 MHz, C_6D_6) δ: 24.54 (CH_2), 26.56 (CH_2), 27.83 (CH_2), 28.84 (CH_3), 39.71 (CH_2), 43.17 (C), 76.76 (CH), 82.94 (CH), 125.18 (2ArCH), 125.69 (2ArCH), 139.55 (ArC), 142.32 (ArC), 167.97 (C=N) ppm. EI-MS (m/z): 291 (M^+). $C_{15}H_{17}NOS_2$: C, 61.82; H, 5.88; N, 4.81. Found: C, 61.80; H, 5.86; N, 4.83. CCDC: 279691.

4.5.5. 2,4-Pentanediol ditosylate (±)-15. Prepared according to the procedure previously reported.[26]

4.5.6. 3,5-Dimethyl-[1,2]-dithiolane (±)-16. A solution of (*d*,*l*)-2,4-pentanediol ditosylate (28.4 g, 69 mmol), sodium sulfite (16.5 g, 69 mmol) and sulfur (2.23 g, 69 mmol) in 180 mL of dimethylformamide was refluxed for 72 h and poured into 300 mL of water and 100 g of ice. The mixture was extracted with petroleum ether (3×50 mL), the organic solution washed with NaCl, dried over $MgSO_4$, filtered and concentrated. The solvent was removed under reduced pressure and the resulting oil was used in the next reaction without any further purification. Spectroscopic data are in accordance with the reported values.

4.5.7. 2,4,6-Trimethyl-1,3-dithiane-2-carboxylic acid (±)-17. To 60 mL of $LiAlH_4$ (solution 1 M in THF, 60 mmol) was added dropwise a solution of (±)-**16** (8.6 g, 64 mmol) in 96 mL of THF. The resulting mixture was refluxed for 2 h and then carefully quenched with 10 mL of H_2SO_4 (1.3 M). The mixture was extracted twice with diethyl ether and the combined organic phase washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the corresponding racemic 2,4-pentanedithiol. Condensation of the dithiol with 8.1 g (92 mmol) of pyruvic acid in 140 mL of benzene containing 0.11 g (0.6 mmol) of *p*-toluenesulfonic acid was performed by refluxing with a Dean–Stark trap until no more water was formed (3 h). The crude was diluted with diethyl ether and $NaHCO_3$ was added. The aqueous layer was acidified to pH 3 with 6 M HCl, extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. The crude was purified on silica gel column chromatography (petroleum ether/EtOAc 4:1) to afford 4.5 g (22 mmol) of the corresponding acid with an overall yield of 35% in two steps. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.23 (3H, d, $J = 6.9$ Hz), 1.46 (3H, d, $J = 7.5$ Hz), 1.76 (3H, s), 1.76–1.83 (1H, m), 1.91–1.96 (1H, m), 3.26–3.33 (1H, m), 3.51–3.63 (1H, m), 9.78 (1H, br s) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 21.03 (CH_3), 21.19 (CH_3), 27.47 (CH_3), 32.57 (CH), 37.92 (CH), 39.91 (CH_2), 50.69 (C), 179.74 (C=O) ppm. EI-MS (m/z): 206 (M^+).

4.5.8. (4*R*,6*R*)- and (4*S*,6*S*)-*N*-[(1*S*)-1-benzyl-2-hydroxyethyl]-2,4,6-trimethyl-1,3-dithiane-2-carboxamide 18. The title compound was obtained following the general procedure for the synthesis of the amide starting from the racemic carboxylic acid (±)-**17**. The two diastereoisomers were separated by column chromatography on silica gel (CH_2Cl_2/EtOAc 5:1) in an overall yield of 50%. *Amide with higher* R_f **18a**: $[\alpha]_D = -28.8$ (c 0.55, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.16 (3H, d, $J = 6.9$ Hz), 1.27 (3H, d, $J = 7.01$ Hz), 1.59 (3H, s), 1.64–1.83 (2H, m), 2.81–2.95 (2H, m), 3.01–3.20 (2H, m), 3.62–3.78 (2H, m), 4.08–4.16 (1H, m), 7.21–7.34 (5H, m) 7.61 (1H, br d, $J = 7.7$ Hz) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 20.93 (CH_3), 21.37 (CH_3), 29.31 (CH_3), 33.45 (CH), 37.19 (CH_2), 37.43 (CH), 40.32 (CH_2), 54.40 (CH), 54.60 (C), 65.00 (CH_2), 127.13 (ArCH), 129.02 (ArCH), 129.40 (ArCH), 129.58 (2ArCH), 137.67 (ArC), 173.90 (C=O) ppm. EI-MS (m/z): 338 (M^+). *Amide with lower* R_f **18b**: $[\alpha]_D = -13.7$ (c 0.52, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (3H, d, $J = 6.9$ Hz), 1.15 (3H, d, $J = 7.37$ Hz), 1.59 (3H, s), 1.62–1.76 (2H, m), 2.64–2.81 (2H, m), 3.00–3.12 (2H, m), 3.61–3.78 (2H, m), 4.09–4.25 (1H, m), 7.20–7.33 (5H, m), 7.53 (1H, br d,

$J = 7.44$ Hz) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 20.86 (CH_3), 21.50 (CH_3), 29.32 (CH_3), 32.50 (CH), 37.05 (CH_2), 37.28(CH), 39.91 (CH_2), 54.53 (CH), 54.75 (C), 65.69 (CH_2), 127.03 (ArCH), 128.89 (ArCH), 128.98 (ArCH), 129.29 (ArCH), 129.47 (ArCH), 137.67 (ArC), 173.89 (C=O) ppm. EI-MS (m/z): 338 (M^+).

4.5.9. (4*S*)-4-Benzyl-2-[(4*R*,6*R*)-2,4,6-trimethyl-1,3-dithian-2-yl]-4,5-dihydro-1,3-oxazole and (4*S*)-4-benzyl-2-[(4*S*,6*S*)-2,4,6-trimethyl-1,3-dithian-2-yl]-4,5-dihydro-1,3-oxazole 19. The title compound was obtained following the general procedure for the synthesis of the oxazoles starting from the corresponding enantiopure amides **18a** and **18b**. *Starting from the amide with higher R_f* **19a**: Yield: 42%. $[\alpha]_D = -37$ (c 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (3H, d, $J = 7.12$ Hz), 1.40 (3H, d, $J = 7.12$ Hz), 1.74 (3H, s), 1.76–1.82 (1H, m), 1.88–1.94 (1H, m), 2.67 (1H, dd, $J = 9.29$ Hz, $J = 13.88$ Hz), 3.19 (1H, dd, $J = 4.86$, $J = 13.34$ Hz), 3.23–3.30 (1H, m), 3.58–3.67 (1H, m), 4.08 (1H, t, $J = 8.23$ Hz), 4.29 (1H, t, $J = 8.56$ Hz), 4.40–4.48 (1H, m), 7.17–7.31 (5H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 21.10 (CH_3), 21.24 (CH_3), 28.74 (CH_3), 33.09 (CH), 37.55 (CH), 40.43 (CH_2), 40.92 (CH_2), 47.45 (C), 67.88 (CH), 73.29 (CH_2), 126.79 (ArCH), 128.76 (ArCH), 128.79 (ArCH), 129.51 (2ArCH), 137.95 (ArC), 170.40 (C=N) ppm. EI-MS (m/z): 321. $C_{17}H_{23}NOS_2$: C, 63.51; H, 7.21; N, 4.36. Found: C, 63.53; H, 7.19; N, 4.33. *Starting from the amide with lower R_f* **19b**: Yield: 48%. $[\alpha]_D = +7$ (c 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (3H, d, $J = 6.78$ Hz), 1.39 (3H, d, $J = 7.52$ Hz), 1.75 (3H, s), 1.76–1.81 (1H, m), 1.88–1.94 (1H, m), 2.64 (1H, dd, $J = 9.45$ Hz, $J = 13.99$ Hz), 3.20 (1H, dd, $J = 4.63$ Hz, $J = 13.89$ Hz), 3.23–3.31 (1H, m), 3.57–3.66 (1H, m), 4.07 (1H, t, $J = 7.74$ Hz), 4.24 (1H, t, $J = 8.57$ Hz), 4.38–4.45 (1H, m), 7.19–7.31 (5H, m) ppm. ^{13}C NMR (75.3 MHz, $CDCl_3$) δ: 20.91 (CH_3), 21.11 (CH_3), 28.69 (CH_3), 33.39 (CH), 37.41 (CH), 40.54 (CH_2), 41.30 (CH_2), 47.53 (C), 67.78 (CH), 72.86 (CH_2), 126.76 (ArCH), 128.76 (2ArCH), 129.56 (2ArCH), 137.84 (ArC), 170.29 (C=N) ppm. EI-MS (m/z): 321. $C_{17}H_{23}NOS_2$: C, 63.51; H, 7.21; N, 4.36. Found: C, 63.52; H, 7.22; N, 4.37.

4.6. General procedure for the preparation of the complex $Cu(OTf)_2$/ligand

In a 10 mL flame dried flask, a solution of $Cu(OTf)_2$ (4 mg, 0.0105 mmol, 2.1 mol %) and the chiral ligand (0.042 mmol, 4.2 mol %) in dry toluene (1 mL) was stirred at room temperature under argon for 1 h. The solvent was removed in vacuo and the residue was analyzed by ESI-MS. *Complex $Cu(OTf)_2$*/**8**: ESI-MS (m/z) = 649 [Cu+2L], 356 [M^+−L], 294 [M^+−L−Cu]. *Complex $Cu(OTf)_2$*/**19a**: ESI-MS (m/z) = 705 [Cu+2L], 384 [M^+−L], 321 [M^+−L−Cu].

4.7. General procedure for the copper catalyzed conjugate addition of Et_2Zn to α,β-unsaturated ketones

In a 10 mL flame-dried flask, a solution of CuOTf (5.4 mg, 0.0105 mmol, 2.1 mol %) and the chiral ligand (0.042 mmol, 4.2 mol %) in dry solvent (1 mL) was stirred at room temperature under argon. After 1 h, the α,β-unsaturated ketone (0.5 mmol) was added. The solution was then cooled to −20 °C and Et_2Zn (0.6 mmol, 0.6 mL of a 1 M solution of diethylzinc in hexane) was added dropwise. The mixture was stirred from 20 to 0 °C for 6 h. The reaction was quenched with HCl 1 M (5 mL) and the aqueous layer was extracted twice with EtOAc (2 × 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. Purification on column chromatography on silica gel afforded the products. *1,3-Diphenyl-1-pentanone*: The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralcel OD column at $\lambda = 254$ nm; flow rate 0. 2 mL/min; eluent: hexane/*i*-PrOH 99.75/0.25, $t_S = 70.30$ min, $t_R = 74.92$ min. *3-Ethylcyclohexanone*: The enantiomeric excess was determined by chiral GC analysis on a Lipodex E column at $T = 60$ °C; $t_R = 23.21$ min, $t_S = 24.48$ min.

4.8. General procedure for palladium catalyzed allylic alkylation

In a 10 mL flame-dried Schlenk, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (4.6 mg, 0.0125 mmol, 2.5 mol %) and the chiral ligand (0.05 mmol, 10 mol %) were dissolved under argon in dry and degassed CH_2Cl_2 (1 mL) and the resulting solution was stirred at room temperature. After 1 h, the 1,3-diphenylprop-3-en-1-yl acetate (126 mg, 0.5 mmol) and dimethyl malonate (198 mg, 1.5 mmol), respectively, in 1 and 0.5 mL of dry and degassed CH_2Cl_2 were added successively, followed by *N*,*O*-(trimethylsilyl)acetamide (BSA, 304 mg, 1.5 mmol, 0.366 mL) and a catalytic amount of potassium acetate (1 mol %). The resulting mixture was stirred at room temperature for 4 h, then the solvent concentrated in vacuo to afford a dark crude. The excess of dimethyl malonate was removed by bulb to bulb distillation (65–75 °C/2 mmHg) and the dark crude mixture was purified by flash chromatography (AcOEt/light petroleum 1/9), to afford 90–98% of product as a colourless oil that solidified on standing. The enantiomeric excess was determined by HPLC analysis on a Daicel Chiralcel AD-H column at $\lambda = 254$ nm; flow rate 0.75 mL/min; eluent: hexane/*i*-PrOH 90/10, $t_R = 17.69$ min, $t_S = 25.00$ min.

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