First Generation Cysteine- and Methionine-Derived Oxazolidine and Thiazolidine Ligands for Palladium-Catalyzed Asymmetric Allylations

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A new series of enantiopure oxazolidine-thioether and thiazolidine-alcohol ligands have been synthesized from L-cysteine, *S*-methyl-L-cysteine, and L-methionine in a straightforward manner that allows numerous structural variations to be formed. These types of ligands have not previously been used in asymmetric palladium-catalyzed allylations and their efficacy was explored in the reaction of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The reaction proceeds in excellent yield and with good enantioselectivity. The palladium catalyst derived from *N*-benzyl-2,2-dimethyl-4-(2-thiapropyl)oxazolidine (**12**) provides the allylation product in a quantitative yield and with an enantiomeric excess of 94%.

Introduction

Palladium-catalyzed reactions have allowed many unique routes to C−C bond formation to be developed, of which a major one is the allylic allylation of carbon nucleophiles.[1] The asymmetric allylic allylation is a widely applied process in which racemic or achiral allylic substrates can be converted into optically active products and has been studied extensively in recent years.[2] Widespread application of this process to the synthesis of small molecules and in the total synthesis of natural products has proven its usefulness.[3] The catalytic activity and enantioselectivity of the reaction is highly dependent on the properties of the chiral ligand, and consequently the design of efficient chiral ligands has become one of the most intensively studied areas of research. In particular, two classes of bidentate ligands, C_2- and C_1-symmetric ones, have been identified. The C_2-symmetric ligands lead to the formation of only one (π-allyl)-palladium complex when a symmetric allylic substrate is used. Nucleophilic attack will take place preferentially at the site at which the allyl functionality has the strongest steric interaction with the ligand. The asymmetric reaction was initially developed by using bidentate ligands with phosphorus as the donor atoms.[4] Many other examples were found due to the excellent ability of phosphorus to stabilize palladium(0);[5] C_2-symmetric bidentate nitrogen-containing ligands have also been investigated extensively.[6] The second class of ligands induces enantioselectivity by another principle. In the presence of a C_1-symmetric ligand, two different (π-allyl)palladium complexes may be obtained, with each one having the possibility of being attacked by the nucleophile at two different sites, leading to four possible transition states in this case. Two effects are responsible for the stereochemical outcome.[7] (1) The electronic effect: if the two donor atoms exhibit sufficiently different donor−acceptor strengths the number of possible transition states is reduced.[8] In general, nucleophilic attack is directed *trans* to the donor atom with the largest π-acceptor strength. (2) The steric effect: the final stereoselectivity is determined by the chiral moiety of the ligand favoring one of the two π-allyl conformations. Various chiral bidentate ligands with two different heterodonor atoms and different donor−acceptor strengths, like (phosphanyl)oxazolines,[9] (phosphanyl)imines,[10] (phosphanyl)amines,[11] phosphite-oxazolines,[12] phosphaferrocene-oxazolines,[13] phosphane-phosphites,[14] (thio)oxazolines,[15] (thio)pyridines,[16] thioglucose-oxazolines,[17] phosphanyl sulfoxides,[18] and phosphito-thioethers,[19] form effective catalysts with palladium to induce high enantioselectivities. To our surprise, heterobidentate sulfur-nitrogen ligands have received little attention in the search for an effective catalyst.

In the course of our work in the field of asymmetric catalysis, we have reported bis(oxazolidinylmetyl) disulfide **4a** (Scheme 1) to be a highly efficient ligand in the enantioselective addition of diethylzinc[20] or alkynylzinc compounds[21] to aldehydes. This ligand affords optically active alcohols, often with excellent enantioselectivity (up to > 99% *ee*).

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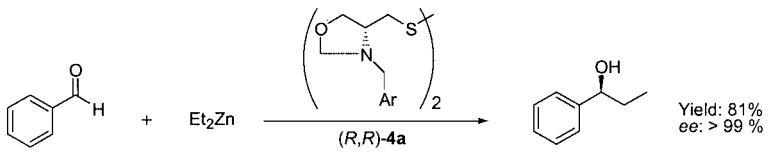


Scheme 1. The enantioselective addition of diethylzinc to benzaldehyde using the disulfide (*R*,*R*)-**4a**

The disulfide **4a** is an attractive catalyst for several reasons. It is derived from cheap L-cysteine, and can be prepared in an easy three-step synthesis (see Scheme 2) in an overall yield of ca. 60%.[20a] Most important, oxazolidines with high structural diversity can be readily generated, which is important for systematic optimization of the catalyst's structure. This type of disulfide is an excellent starting point in the synthesis of a variety of sulfur-oxazolidine ligands by a general combinatorial approach (Figure 1).[22] The objective of this work was to screen the catalytic potential of sulfur-containing ligands in various homogeneous catalytic reactions. Owing to the soft nature of the sulfur atom we focused our efforts on the reactions of the late transition metals. The palladium-catalyzed allylic alkylation attracted our attention because the use of C_1 bidentate ligands with an oxazoline unit as the chiral modifier in this reaction has been investigated extensively, and proved to be very successful. In contrast, to the best of our knowledge, heterobidentate ligands with a similar oxazolidine unit have not yet been investigated.

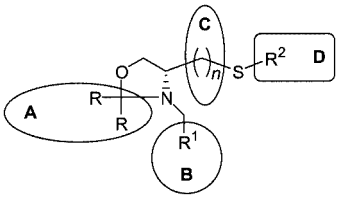
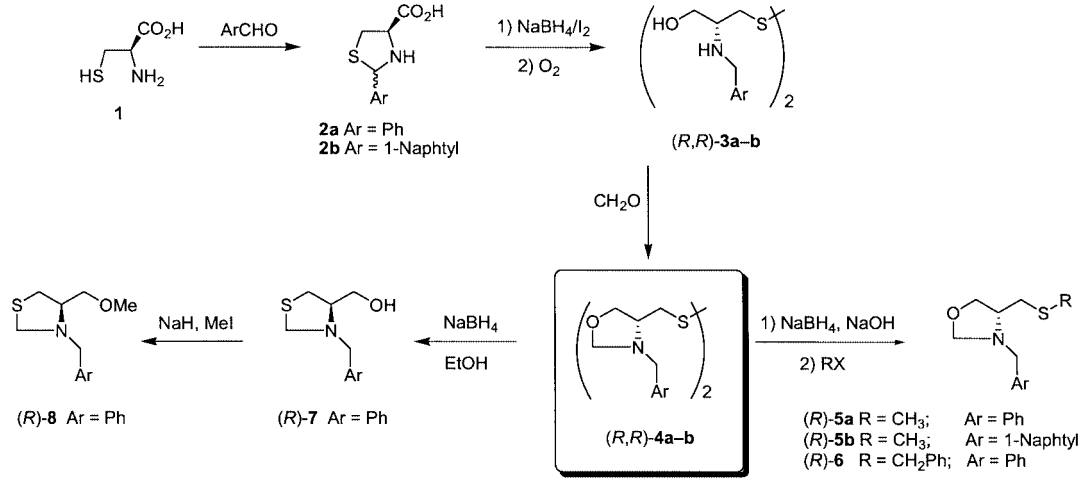


Figure 1. General combinatorial approach to the synthesis of sulfur-oxazolidine ligands with the variables R and *n* (**A**−**D**)

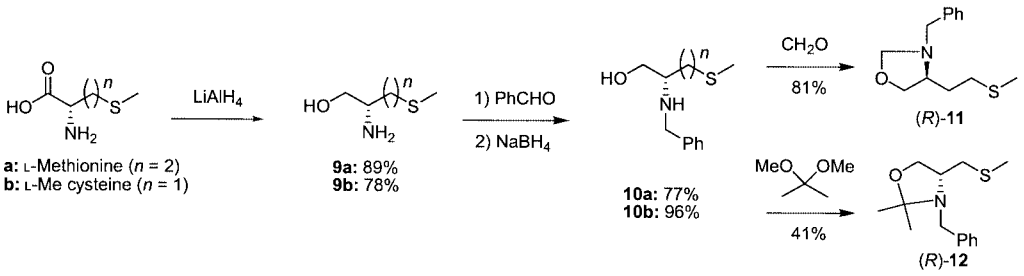
Results and Discussion

The successful results that were obtained with the disulfide **4a** prompted us to explore the potential of **4** and some first-generation derivatives. A series of new heterobidentate sulfur-oxazolidine ligands with variations in R^1 and R^2 (**B** and **D**, Figure 1), derived from the disulfides **4**, were synthesized to enable a systematic improvement of the ligand's structure (Scheme 2).[23] A simple transformation of **4a** into the thioethers **5a** (93% yield) and **6** (64% yield) was achieved by $NaBH_4$ reduction under basic conditions and consecutive alkylation with MeI and benzyl chloride, respectively. By using the *N*-(1-naphthylmethyl) derivative **4b**, an analogous procedure can be followed to give **5b** in 69% yield. Reduction of bis(oxazolidinylmethyl) disulfide **4a** with $NaBH_4$ under neutral conditions, however, gave the thiazolidine alcohol **7** exclusively in 80% yield and not the expected free thiol. Methylation of **7** with sodium hydride and methyl iodide resulted in the methyl thiazolidinylmethyl ether **8** in 47% yield.

Another, more efficient strategy was developed to obtain variations in R and *n* (**A** and **C**, Figure 1). Starting from L-methionine or *S*-methyl-L-cysteine, instead of L-homocysteine and L-cysteine, reduces the number of steps in the synthesis of (*S*)-methyloxazolidines with one- and two-carbon tethers (Scheme 3). Reduction, followed by benzylation and cyclization, resulted in an overall yield of 56% of **11**. Thioether **12**, an analogue of thioether **5a** with more steric hindrance at the 2-position of the oxazolidine, was obtained in a similar three-step synthesis (Scheme 3) in a moderate overall yield of 31%.



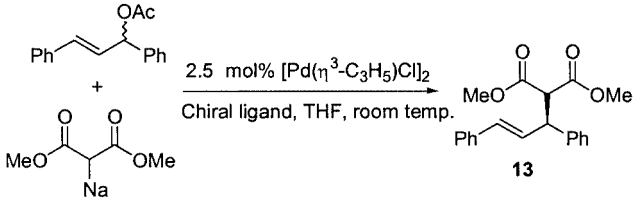
Scheme 2. Synthesis of sulfur-oxazolidine ligands by the general combinatorial approach



Scheme 3. Synthesis of ligands with variations in R or *n* (**A** and **C**, Figure 1)

The reaction of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate as the nucleophile is the standard reaction that is used to test the potential of a ligand in the asymmetric palladium-catalyzed allylic alkylation. The reaction was performed with dimethyl sodiomalonate, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), disulfide **4a** (10 mol %), and THF as solvent at room temperature. Unfortunately, the reaction with this ligand was not successful; a moderate 63% yield of an almost racemic product was obtained (Table 1, Entry 1). Sulfur-sulfur coordination to palladium might be the reason for the low enantioselectivity.[9a]

Table 1. Asymmetric palladium-catalyzed allylic alkylation



Entry[a]	Ligand	Time [h]	Yield [%][b]	*ee* [%][c]
1	**4a** (10 mol %)	48	63	6 (*S*)
2	**5a** (5 mol %)	20	84	62 (*S*)
3	**5a** (10 mol %)	12	96	71 (*S*)
4	**5a** (15 mol %)	15	94	60 (*S*)
5	**5b** (10 mol %)	15	97	69 (*S*)
6	**6** (10 mol %)	15	96	70 (*S*)
7	**7** (5 mol %)	168	43	–
8	**7** (10 mol %)	168	52	81 (*S*)
9	**7** (15 mol %)	169	61	74 (*S*)
10	**8** (10 mol %)	64	59	31 (*S*)
11	**11** (10 mol %)	24	87	6 (*S*)
12	**12** (10 mol %)	12	96	81 (*S*)

[a] NaH (1.5 equiv.), dimethyl malonate (2 equiv.), and 1,3-diphenyl-2-propenyl acetate (1 equiv.). [b] Isolated yield. [c] Determined by HPLC using a Daicel Chiralcel OD-H column; solvent: hexane/2-propanol (99:1); flow rate: 0.5 mL·min^{-1}; UV detection: 254 nm. The absolute configuration of the product was assigned by comparison of the sign of the specific rotations with literature data.[9b]

This prompted us to screen oxazolidine-thioether **5a**. A 5 mol % loading of **5a**, which corresponds to a 1:1 ratio of bidentate ligand/palladium, resulted in 84% yield and a modest enantiomeric excess of 62% (Table 1, Entry 2). The ligand/palladium ratio was increased because it is known that heterobidentate sulfur-nitrogen ligands do not always bind efficiently to palladium, and competition for coordination of the solvent might result if the ligand concentration is insufficient.[14] However, in our system, an increased ratio of 2:1, apparently has only a small influence, resulting in only a slightly improved enantiomeric excess of 71% (Table 1, Entry 3); this implies good binding of **5a** to palladium. The decrease in enantioselectivity that occurs with a 3:1 ratio (Table 1, Entry 4) might be caused by a change in the mode of coordination of the ligands to palladium; two monodentate coordinating ligands instead of a single bidentate coordinating ligand is a possible explanation.

The screening process was continued by using the optimum 2:1 ratio (ligand/palladium) and benzyl thioether **6** (Table 1, Entry 6) in order to study the influence of a slightly bulkier substituent at the sulfur atom (**D**, Figure 1). The reactions with benzyl thioether **6** (70% *ee*) and methyl thioether **5a** (71% *ee*) resulted in the same enantiomeric excess. This indicates that the oxazolidine moiety is mainly responsible for the enantioselectivities that are obtained. The 1-naphthylmethyl derivative **5b** was tested in an attempt to increase the steric bulk around the nitrogen donor (**B**, Figure 1). Unfortunately, this variation did not result (97% yield, 69% *ee*) in any significant change in the properties of the respective palladium complex (Table 1, Entry 5). The enantiomeric excesses were the same with the thioethers **5** and **6**. Obviously other or more dramatic structural changes are required at the nitrogen or sulfur atom to increase the enantiomeric excess that can be obtained with this type of ligand.

Reactions with thiazolidinylmethanol **7** and thiazolidinylmethyl ether **8** enable the influence of the donor-atom distribution in the ligand to be studied. The alkylation products had the same absolute (*S*) stereochemistry as was obtained with thioethers **5** and **6**, but with an increased enantiomeric excess of 81% with alcohol **7** (Table 1, Entry 8) and a decreased enantiomeric excess of 31% with ether **8** (Table 1, Entry 10). Thiazolidines **7** and **8** probably also act as bidentate ligands and form oxygen-nitrogen complexes with palladium. However, the direction of the nucleophilic attack is different compared with that at the nitrogen-sulfur palladium complexes. Coincidentally, the increase in enantioselectivity with **7** was achieved by using 10 mol % of the

ligand (2:1 ratio) (Table 1, Entry 8). However, when a 1:1 ratio of bidentate ligand/palladium was used, a racemic product was observed in only 43% yield. This indicates that this ligand probably does not bind strongly to the metal atom. The decrease in enantioselectivity observed with a 3:1 ratio (Table 1, Entry 9) was similar to that obtained when the heterobidentate sulfur-nitrogen ligand **5a** was used (Table 1, Entry 4). The large difference between the donor−acceptor strengths of oxygen and sulfur explains the poor yields and long reaction times of **7** compared with the complete conversion that occurred with thioether **5a** after 12 h.

The low catalytic activity of the thiazolidinylmethanol ligands led us to develop the oxazolidine-thioether ligand structure further. The importance of the bite angle (Figure 2, complexes **14** and **15**) in the asymmetric palladium-catalyzed allylic alkylation has been generally accepted as the chiral environment of the ligand has to reach over the palladium atom in order to interact with the allylic unit. Increased interactions between the ligand and allylic unit can result in greater enantioselectivity. An increase in the tether length between the two donor atoms of the bidentate ligand can increase the bite angle. A three- instead of a two-carbon tether was highly favorable for the oxazoline-thioether ligands described previously (C_2: *ee* = 56%: C_3: *ee* = 88%).[15c] Unfortunately, the larger bite angle had an opposite effect in our case; the enantiomeric excess decreased to 6% with the larger oxazolidine-thioether **11**. This low enantioselectivity might be explained by the lower rigidity of the oxazolidine ring compared to the oxazoline ring. Other explanations are possible, such as the ability to form additional chiral centers at the nitrogen and sulfur atoms when complexed to the palladium center,[17,24] and the higher flexibility of the benzyl substituent on the oxazolidine unit compared to the phenyl substituent on the oxazoline ligands that have been studied (Figure 2, complexes **15** vs. **16**).

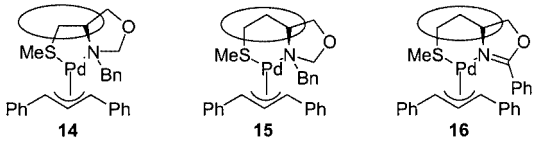


Figure 2. The bite angle effect

The successful application of heterobidentate ligands in this reaction originates from steric and electronic effects (Figure 3). The enantiodifferentiation step in palladium-catalyzed allylic alkylations is the substitution of (allyl)Pd complexes by incoming nucleophiles. Nucleophilic attack occurs predominantly at the allyl terminus *trans* to the better π-acceptor. The sulfur donor has a greater *trans* influence (greater π-acceptor capacity) than the nitrogen donor, and therefore directs the incoming nucleophile *cis* to the nitrogen atom.[25] This electronic effect is supported by the enantioselectivities observed with thioethers **5a** and **6**, and implies that the oxazolidine unit controls the enantioselectivity (steric effect). With alcohol **7** and ether **8** the opposite absolute stereochemistry would be expected if oxygen was a stronger π-acceptor than nitrogen. This is not the case, and the nitrogen donor directs nucleophilic attack *cis* to the oxygen donor, which explains why the absolute configurations of the alkylation products are the same for thiazolidine-oxygen and oxazolidine-sulfur ligands. The strongly diminished enantioselectivity obtained with methyl ether **8** might be the result of a less pronounced difference between the π-acceptor strengths of the thiazolidine-nitrogen and the ether-oxygen, such that the incoming nucleophile exerts less directional preference.

The stereochemical course of the reaction with oxazolidine ligands can proceed via the two diastereomeric (allyl)-palladium complexes **17** and **18** (Figure 3). The (*S*) enantiomer is formed in excess, which could be the result of nucleophilic attack *trans* to the oxazolidine moiety in the M-shaped complex **17** or *trans* to the thioether in the W-shaped complex **18**. From previous results, it can be concluded that the nucleophilic attack most likely occurs via complex **18**, *trans* to the thioether. The M-shaped complex **17** suffers from steric hindrance between the rather rigid oxazolidine moiety and the phenyl group of the allylic substrate. In the W-shaped complex **18** there is less steric hindrance between the allylic phenyl and the more flexible benzyl group. As a consequence alterations at the oxazolidine moiety should allow the stereochemical outcome of the allylic alkylation to be controlled.

With this in mind we tested the 2,2-dimethyloxazolidine **12**, an analogue of thioether **5a** with more steric crowding of the oxazolidine ring. As expected, a significant increase in enantioselectivity to 81% *ee* was observed, together with complete conversion after 12 h (Table 1, Entry 12).

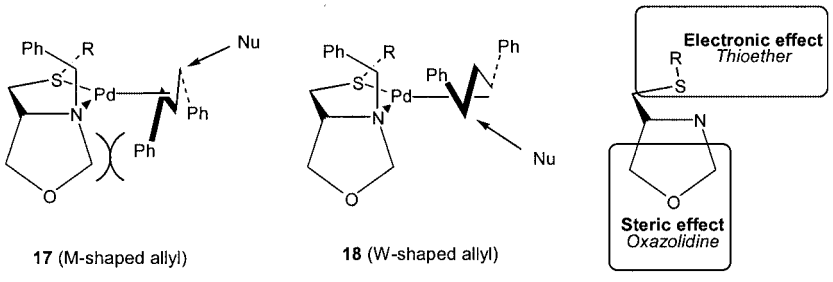
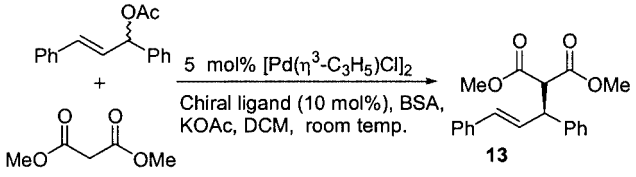


Figure 3. Diastereomeric (allyl)palladium complexes; enantioselectivity as a result of steric and electronic effects

Substitution of the previously used dimethyl sodiomalonate procedure by a facile one-pot procedure with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate, led to an increase in the rate of the reaction as well as in chiral induction.[15d,15e] The potential of disulfide **4a** seems to be somewhat higher under these conditions with an *ee* of 20% (Table 2, Entry 1), but is still very poor compared with the high enantioselectivities obtained with this ligand in the addition of organozinc compounds to aldehydes. An increased catalytic activity was observed with the ligands **5a**, **5b**, **7** and **12**, which might be explained by the better solubility of the in situ generated nucleophile relative to dimethyl sodiomalonate. A general effect on the enantiomeric excess was not observed. There was no effect on the enantioselectivity with ligands **5** and **6**. The enantioselectivity of **11** increased substantially, but is still very low. A significant decrease in *ee* from 81% to 59% was observed with thiazolidinylmethanol **7** (Table 2, Entry 5), and from 31% to 21% for thiazolidinylmethyl ether **8** (Table 2, Entry 6). Fortunately, this catalytic system had a positive effect on thioether **12**, with an enantiomeric excess of 94% (Table 2, Entry 8), the highest obtained with these oxazolidinylmethyl thioether ligands.

Table 2. One-pot asymmetric palladium-catalyzed allylic substitution of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate



Entry[a]	Ligand	Time [h]	Yield [%][b]	*ee* [%][c]
1	**4a**	24	28	20 (*S*)
2	**5a**	6	96	68 (*S*)
3	**5b**	8	96	69 (*S*)
4	**6**	15	95	68 (*S*)
5	**7**	48	48	59 (*S*)
6	**8**	64	56	21 (*S*)
7	**11**	15	93	17 (*S*)
8	**12**	10	98	94 (*S*)

[a] *N*,*O*-Bis(trimethylsilyl)acetamide (BSA, 3 equiv.), dimethyl malonate (3 equiv.), KOAc (0.06 mmol), and acetate (1 equiv.). [b] Isolated yield. [c] Determined by HPLC using a Daicel Chiralcel OD-H column; solvent: hexane/2-propanol (99:1); flow rate: 0.5 mL·min^{-1}; UV detection: 254 nm. The absolute configuration of the product was assigned by comparison of the sign of the specific rotations with literature data.[9b]

Conclusions

In summary, some new, enantiopure oxazolidinylmethyl thioether and thiazolidinylmethanol ligands have been efficiently synthesized from readily available amino acids, like L-cysteine, *S*-methyl-L-cysteine, and L-methionine. Promising preliminary results from asymmetric palladium-catalyzed allylic alkylations have been obtained, and these results will allow the design of improved ligands of this type, adapted for application in palladium-catalyzed reactions, including carbon−carbon and carbon−heteroatom bond formations. Subtle changes in the ligand's structure made it possible to clarify the mode of action, determine a ligand structure−catalyst efficiency relationship, and to undertake a rational improvement of the ligand's structure. This shows the importance of a flexible synthetic strategy for systematic optimization of the catalyst's structure, and an enantiomeric excess of 94% was obtained by increasing the steric bulk at the 2-position of the oxazolidine. Interestingly, for thiazoline-oxygen ligands, nucleophilic attack does not need to take place near the chiral modifier to obtain enantioselective reactions.

Experimental Section

General: The reagents and solvents were purchased from Sigma−Aldrich and used without purification. All reactions were performed under argon unless otherwise stated. Silica gel (230−400 mesh) was used as the stationary phase in flash chromatography. Optical rotations were measured with a Perkin−Elmer 341 polarimeter. The NMR spectra were recorded with a Varian Mercury 300 or 400 MHz spectrometer using TMS as the internal standard. Chemical shifts δ are quoted in parts per million (ppm), and coupling constants *J* are given in Hertz (Hz). IR spectra were recorded in the range of 4000−600 cm^{-1} using a Nicolet Magna 550 spectrometer, and were measured as KBr or as neat oils. HPLC analyses were carried out with a Shimadzu SCL-10 AVP chromatograph using a Diacel Chiralcel OD column; solvent: hexane/2-propanol (99:1); flow rate: 0.5 mL·min^{-1}; UV detection: 254 nm. Elemental analyses were performed with a Leco CHNS-932 analyzer. High-resolution mass spectra were recorded with a Bruker BioApex 70e FT-ICR (Bruker Daltonics, Billerica, USA) instrument in ESI mode and with a GCT (Micromass, Manchester, UK) instrument in EI mode (70 eV). The spectral data of the known compounds **2a**, **3a**, **4a**,[20a] and **12**, **17**[15e] are in accordance with the literature data.

General Procedure for the Allylic Alkylation of 1,3-Diphenyl-2-propenyl Acetate with Dimethyl Sodiomalonate: A THF (1 mL) solution of [Pd(η^3-C_3H_5)Cl]$_2$ (9 mg, 25 μmol, 2.5 mol %), and ligand (**1**, **3**−**6**, 10 mol %) was stirred for 30 min under argon and then *rac*-1,3-diphenyl-2-propenyl acetate (252 mg, 1.0 mmol) was added. The mixture was stirred for 10 min and a solution of dimethyl sodiomalonate, prepared from dimethyl malonate (264 mg, 2.0 mmol) and sodium hydride (36 mg, 1.5 mmol) in THF (3 mL), was added at room temperature. The mixture was stirred at room temperature for the time given in Table 1. The reaction was quenched with saturated NH_4Cl (aq.) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried with $MgSO_4$. The solvent was evaporated and the crude product purified by flash chromatography on silica gel (230−400 mesh) with hexane/ethyl acetate (98:2) as eluent.

General Procedure for the Allylic Alkylation of 1,3-Diphenyl-2-propenyl Acetate with Dimethyl Malonate: A solution of [PdCl(η^3-C_3H_5)]$_2$ (18 mg, 50 μmol, 5 mol %), and chiral ligand (0.1 mmol, 10 mol %) in dichloromethane (1.5 mL) was stirred for 30 min at room temperature. Subsequently, a solution of *rac*-1,3-diphenyl-2-propenyl acetate (252 mg, 1.0 mmol), dimethyl malonate (480 mg,

3.0 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (608 mg, 3.0 mmol), and KOAc (3 mg, cat. quantity) in dichloromethane (0.8 mL) were added. The reaction mixture was stirred for the time presented in Table 2. Satd. NH_4Cl (aq.) was then added to quench the reaction, followed by extraction with dichloromethane (3 × 15 mL). The combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo and the product purified by flash chromatography on silica gel (230−400 mesh) with hexane/ethyl acetate (98:2) as eluent.

(4*R*)-2-Naphthyl-1,3-thiazolidine-4-carboxylic Acid (2b): 1-Naphthaldehyde (4.68 g, 30 mmol) diluted in ethanol (30 mL) was added to a solution of (*R*)-cysteine (3.63 g, 30 mmol) in water (40 mL). The product thiazolidine **2b** soon began to drop out of solution. The reaction was kept at 25 °C for 3 h and at 0 °C for an additional 3 h. The product was filtered, washed with ethanol, and dried to afford 6.78 g (88%) of a diastereomeric mixture of **2b** as a white powder. IR (KBr): $\tilde{\nu}$ = 1609, 1554, 1367, 774 cm^{-1}. ^1H NMR (300 MHz, [D$_6$]DMSO, isomer A): δ = 8.20 (d, *J* = 8.06 Hz, 1 H), 7.98−7.47 (m, 6 H), 6.29 (s, 1 H), 4.11 (dd, *J* = 8.78, 7.13 Hz, 1 H), 3.47 (dd, *J* = 9.97, 7.13 Hz, 1 H), 3.15 (m, 1 H); isomer B: δ = 8.14 (d, *J* = 8.24 Hz, 1 H), 7.98−7.47 (m, 6 H), 6.45 (s, 1 H), 4.29 (dd, *J* = 6.32, 6.32 Hz, 1 H), 3.33 (dd, *J* = 10.16, 6.32 Hz, 1 H), 3.15 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 172.71 (172.10), 136.92, 134.36, 133.17, 133.02, 130.50, 130.27, 128.42, 128.29, 127.62, 126.17, 125.99, 125.76, 125.59, 125.32, 125.21, 123.42, 123.37, 123.21, 122.16, 67.91 (68.25), 64.95 (65.18), 37.81 (37.99) ppm. HRMS-ESI : *m*/*z* calcd. for $C_{14}H_{14}NO_2S$ 260.0739 [M + H^+]; found 260.0725. $C_{14}H_{13}NO_2S$ (259.3): calcd. C 64.84, H 5.05; found C 64.80, H 5.09. $[\alpha]_D^{25}$ = −159.1 (*c* = 0.6, CH_3OH).

Bis[(2*R*)-2-{[(1-naphthyl)methyl]amino}-3-hydroxypropyl] Disulfide (3b): A solution of iodine (5.08 g, 20.0 mmol) in THF (20 mL) was added slowly to a suspension of **2b** (5.18 g, 20.0 mmol) and $NaBH_4$ (1.90 g, 50.0 mmol) in THF (50 mL) at room temperature. After the addition was complete, the reaction mixture was refluxed for 20 h and then cooled to room temperature. Methanol was added to the mixture until a clear solution was obtained. The solvent was removed in vacuo and the residue dissolved in 20% K_2CO_3 (aq.) (50 mL). The mixture was stirred at room temperature for 4 h. After extraction with dichloromethane (3 × 30 mL), the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo. The crude product was crystallized from methanol/diethyl ether to yield 5.20 g (53%) of **3b** as a white powder. IR (KBr): $\tilde{\nu}$ = 3294, 2911, 2850, 791, 775 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.17 (m, 2 H), 7.88 (m, 2 H), 7.79 (d, *J* = 7.8 Hz, 2 H), 7.52−7.38 (m, 8 H), 4.71 (m, 2 H), 4.21 (d, *J* = 13.1 Hz, 2 H), 4.15 (d, *J* = 13.1 Hz, 2 H), 3.57−3.46 (m, 4 H), 2.97−2.90 (m, 6 H), 2.06 (br. s, 2 H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 136.2, 133.1, 131.2, 128.1, 127.1, 125.7, 125.6, 125.4, 125.2, 124.0, 61.9, 58.7, 48.5, 41.0 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{28}H_{33}N_2O_2S_2$ 493.1977 [M + H^+]; found 493.1975. $[\alpha]_D^{25}$ = −99.98 (*c* = 0.50, $CHCl_3$).

Bis[{(4*R*)-3-[(1-naphthyl)methyl]-1,3-oxazolidin-4-yl}methyl] Disulfide (4b): Benzene (30 mL), **3b** (1.50 g, 3.05 mmol), paraformaldehyde (275 mg, 9.15 mmol), and *p*-toluenesulfonic acid (cat. amount) were added to a 50-mL round-bottomed flask equipped with a Dean−Stark apparatus. The mixture was refluxed for 5 h and then cooled to room temperature. The benzene was removed in vacuo, the residue dissolved in dichloromethane (30 mL), and washed with 0.5 N NaOH (aq.). The organic layer was dried with $MgSO_4$, filtered, and the solvent removed in vacuo to afford 1.48 g (94%) of **4b** as a brown oil. IR (film): $\tilde{\nu}$ = 2923, 2868, 1514, 1454, 1354, 1154, 1094, 1039, 871, 805 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.30−8.28 (m, 2 H), 7.90−7.81 (m, 4 H), 7.50−7.38 (m, 8 H), 4.30 (d, *J* = 5.9 Hz, 2 H), 4.15−4.00 (m, 8 H), 3.98−3.36 (m, 4 H), 2.71 (dd, *J* = 13.3, 6.5 Hz, 2 H), 2.57 (dd, *J* = 13.3, 6.8 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 134.02, 133.70, 131.95, 128.32, 128.21, 127.28, 126.18, 125.85, 124.99, 124.60, 85.40, 68.96, 62.75, 57.02, 41.83 ppm. HRMS-EI: *m*/*z* calcd. for $C_{15}H_{16}NOS_2$ 291.0714 [M − $C_{15}H_{16}NO]^+$; found 291.0733. $[\alpha]_D^{25}$ = −24.95 (*c* = 0.413, $CHCl_3$).

(4*R*)-*N*-Benzyl-4-[(methylthio)methyl]-1,3-oxazolidine (5a): $NaBH_4$ (114 mg, 3.00 mmol) was added in portions to a solution of disulfide **4a** (630 mg, 1.50 mmol) and NaOH (114 mg, 2.85 mmol) in dry ethanol (10 mL) at room temperature. The reaction mixture was stirred for 30 min and then MeI (374 μL, 6.00 mmol) was added. After 2 h, the ethanol was evaporated and the residue dissolved in CH_2Cl_2 (30 mL), washed with water, and dried with $MgSO_4$. Removal of the solvent in vacuo and purification by flash chromatography on silica gel (230−400 mesh) with hexane/ethyl acetate (85:15) as eluent afforded 622 mg (93%) of **5a** as an oil. IR (film): $\tilde{\nu}$ = 2915, 2860, 1495, 1454, 1356, 1247, 1154, 744, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40−7.20 (m, 5 H), 4.35 (d, *J* = 5.7 Hz, 1 H), 4.32 (d, *J* = 5.7 Hz, 1 H), 4.10 (dd, *J* = 7.0, 8.4 Hz, 1 H), 3.82 (d, *J* = 13.0 Hz, 1 H), 3.75 (d, *J* = 13.0 Hz, 1 H), 3.54 (dd, *J* = 5.2, 8.4 Hz, 1 H), 3.20 (m, 1 H), 2.64 (dd, *J* = 5.8, 13.1 Hz, 1 H), 2.44 (dd, *J* = 8.5, 13.1 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.7, 128.7, 128.3, 127.2, 86.0, 69.4, 62.7, 59.0, 37.9, 15.8 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{12}H_{17}NOSNa$ 246.0924 [M + Na]$^+$; found 246.0923. $C_{12}H_{17}NOS$ (223.3): calcd. C 64.53, H 7.67; found C 64.47, H 7.81. $[\alpha]_D^{25}$ = −39.7 (*c* = 1.12, CH_3OH).

(4*R*)-4-[(Methylthio)methyl]-3-[(1-naphthyl)methyl]-1,3-oxazolidine (5b): The experimental procedure that was used to prepare **5a** was applied but by using disulfide **4b** (774 mg, 1.50 mmol) instead of **4a**. Oxazolidine **5b** was obtained as an oil in 63% yield (493 mg). IR (film): $\tilde{\nu}$ = 2914, 2865, 1596, 2509, 1151, 1096, 1000, 792, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.37 (dd, *J* = 7.96, 1.00 Hz, 1 H), 7.86−7.78 (m, 2 H), 7.57−7.25 (m, 4 H), 4.43 (d, *J* = 5.95 Hz, 1 H), 4.29 (d, *J* = 5.95 Hz, 1 H), 4.24−4.14 (m, 3 H), 3.56 (dd, *J* = 8.42, 5.21 Hz, 1 H), 3.36 (m, 1 H), 2.62 (dd, *J* = 13.08, 6.13 Hz, 1 H), 2.44 (dd, *J* = 13.08, 8.38 Hz, 1 H), 2.01 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz): δ = 134.18, 133.69, 131.99, 128.33, 128.23, 127.23, 125.89, 125.66, 125.00, 124.58, 85.52, 69.46, 63.41, 57.33, 38.12, 16.10 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{16}H_{19}NOSNa$ 296.1081 [M + Na]$^+$; found 296.1079. $C_{16}H_{19}NOS$ (273.4): calcd. C 70.29, H 7.00; found C 70.07, H 6.97. $[\alpha]_D^{25}$ = −18.35 (*c* = 0.5, $CHCl_3$).

(4*R*)-3-Benzyl-4-[(benzylthio)methyl]oxazolidine (6): An experimental procedure identical to that used for the preparation of **5a** was applied using benzyl bromide instead of methyl iodide and disulfide **4a** (630 mg, 1.50 mmol). Product **6** was obtained as an oil in a yield of 69% (309 mg). IR (film): $\tilde{\nu}$ = 3027, 2866, 1494, 1453, 1005, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.00 (m, 10 H), 4.13 (s, 2 H), 3.85 (dd, *J* = 7.2, 8.2 Hz, 1 H), 3.58 (d, *J* = 13.0 Hz, 1 H), 3.52 (d, *J* = 13.0 Hz, 1 H), 3.45 (s, 2 H), 3.31 (dd, *J* = 5.2, 8.2 Hz, 1 H), 2.94 (m, 1 H), 2.40 (dd, *J* = 5.9, 13.1 Hz, 1 H), 2.18 (dd, *J* = 8.6, 13.1 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.8, 138.3, 128.8, 128.7, 128.4, 128.3, 127.3, 126.9, 86.1, 68.9, 62.4, 58.7, 36.0, 34.4 ppm. HRMS-EI: *m*/*z* calcd. for $C_{18}H_{21}NOS$ 299.1344 [M$^+$]; found 299.1408. $C_{18}H_{21}NOS$ (299.4): calcd. C 72.20, H 7.07; found C 72.07, H 7.08. $[\alpha]_D^{25}$ = +28.74 (*c* = 0.526, $CHCl_3$).

[(4*R*)-3-Benzyl-1,3-thiazolidin-4-yl]methanol (7): A solution of disulfide **4a** (420 mg, 1.0 mmol) in dry ethanol (10 mL) was cooled to 0 °C. $NaBH_4$ (114 mg, 3.0 mmol) was added and the reaction mixture stirred at room temperature for 1 h. The reaction was quenched with brine, followed by extraction with CH_2Cl_2. The organic layer was washed with brine and dried with $MgSO_4$. The solvent was evaporated and the crude product purified by distillation (100 °C, 4 Torr), which afforded alcohol **7** as an oil in 80% yield (334 mg). IR (film): $\tilde{\nu}$ = 3408, 2940, 2879, 1045, 1025, 733, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30−7.05 (m, 5 H), 3.85 (d, *J* = 10.3 Hz, 1 H), 3.75 (d, *J* = 10.3 Hz, 1 H), 3.50 (d, *J* = 13.0 Hz, 1 H), 3.45 (m, 1 H), 3.38 (d, *J* = 13.0 Hz, 1 H), 3.24−3.10 (m, 2 H), 2.86 (dd, *J* = 6.9, 10.7 Hz, 1 H), 2.44 (dd, *J* = 1.8, 10.7 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.0, 128.8, 128.3, 127.4, 69.8, 61.5, 58.2, 56.9, 31.3 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{11}H_{16}NOS$ 210.0947 $[M + H]^+$; found 210.0942. $[\alpha]_D^{25}$ = −84.96 (*c* = 0.453, $CHCl_3$).

(4*R*)-3-Benzyl-4-(methoxymethyl)-1,3-thiazolidine (8): NaH (72 mg, 3.0 mmol) was added in portions to a solution of alcohol **7** (627 mg, 3.0 mmol) at 0 °C. The mixture was stirred at room temp. for 15 min and MeI (374 μL, 6.0 mmol) was then added. After 2 h, brine was added, followed by extraction with CH_2Cl_2. The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo. The crude product was purified by column chromatography (silica; ethyl acetate/hexane, 15:85) to afford 47% (314 mg) of **8** as an oil. IR (film): $\tilde{\nu}$ = 2927, 2881, 2813, 1452, 1109, 733, 692 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39−7.23 (m, 5 H), 4.08 (d, *J* = 10.07 Hz, 1 H), 3.98 (d, *J* = 10.06 Hz, 1 H), 3.69−3.57 (m, 3 H), 3.37 (dd, *J* = 9.52, 6.22 Hz, 1 H), 3.33 (s, 3 H), 3.22 (dd, *J* = 9.52, 7.50 Hz, 1 H), 3.04 (dd, *J* = 10.61, 6.40 Hz, 1 H), 2.87 (dd, *J* = 10.61, 2.74 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.08, 128.81, 128.23, 127.21, 73.17, 67.66, 58.94, 58.82, 58.18, 31.99 ppm. HRMS-EI: *m*/*z* calcd. for $C_{12}H_{17}NOS$ 223.1031 $[M]^+$; found 223.1072. $[\alpha]_D^{25}$ = −97.01 (*c* = 0.513, $CHCl_3$).

(2*R*)-2-(Benzylamino)-4-(methylthio)butan-1-ol (10a): Benzaldehyde (1.3 mL, 11.2 mmol) was added to a cooled solution of amino alcohol **9a** (1.5 g, 11.1 mmol) in dry methanol (15 mL). The reaction mixture was stirred at room temp. for 1 h, cooled to 0 °C and $NaBH_4$ (850 mg, 22.4 mmol) was added in portions over 30 min. Next, 4 M HCl (aq.) (15 mL) and diethyl ether (20 mL) were added. The organic layer was washed twice with 4 M HCl (aq.). The combined aqueous layers were extracted with diethyl ether and the combined ethereal layers were discarded. The aqueous layer was neutralized with $NaHCO_3$ and extracted three times with diethyl ether. The organic layers were combined and dried with $MgSO_4$ and the solvent removed in vacuo to afford pure **10a** as an oil in 77% (1.92 g) yield. IR (KBr): $\tilde{\nu}$ = 3261, 2915, 2852, 1451, 1061, 733, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35−7.23 (m, 5 H), 3.84 (d, *J* = 12.99 Hz, 1 H), 3.78 (d, *J* = 12.99 Hz, 1 H), 3.67 (dd, *J* = 10.98, 3.84 Hz, 1 H), 3.39 (dd, *J* = 10.98, 5.86 Hz, 1 H), 2.85 (m, 1 H), 2.63 (br. s, 2 H), 2.53 (m, 2 H), 2.09 (s, 3 H), 1.79 (m, 2 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.33, 128.38, 128.09, 127.14, 62.49, 57.46, 50.86, 30.86, 30.70, 15.62 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{12}H_{20}NOS$ 226.1260 $[M + H]^+$; found 226.1257. $C_{12}H_{19}NOS$ (225.3): calcd. C 63.96, H 8.50; found C 63.47, H 8.21. $[\alpha]_D^{25}$ = +25.49 (*c* = 0.453, $CHCl_3$).

(4*R*)-3-Benzyl-4-[2-(methylthio)ethyl]oxazolidine (11): An experimental procedure similar to that used for the preparation of **4b** was applied using amino alcohol **10a** (1.35 g, 6.0 mmol), paraformaldehyde (270 mg, 9.0 mmol), benzene (80 mL) and *p*-toluenesulfonic acid (cat. amount). Product **11** was obtained as an oil in a yield of 81% (1.29 g). IR (film): $\tilde{\nu}$ = 2913, 2864, 1494, 1453, 1436, 1153, 1010, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.22 (m, 5 H), 4.34 (d, *J* = 6.03 Hz, 1 H), 4.29 (d, *J* = 6.03 Hz, 1 H), 4.08 (dd, *J* = 7.87, 7.13 Hz, 1 H), 3.73 (s, 2 H), 3.35 (dd, *J* = 8.05, 4.94 Hz, 1 H), 3.20 (m, 1 H), 2.60−2.38 (m, 2 H), 2.03 (s, 3 H), 1.77 (m, 1 H), 1.57 (m, 1 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 138.85, 128.78, 128.18, 127.11, 85.49, 69.12, 62.22, 59.22, 33.01, 31.25, 15.51 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{13}H_{20}NOS$ 238.1259 $[M + H]^+$; found 238.1260. $C_{13}H_{19}NOS$ (237.4): calcd. C 65.78, H 8.07; found C 65.64, H 7.81. $[\alpha]_D^{25}$ = −26.81 (*c* = 0.593, $CHCl_3$).

(2*R*)-2-(Benzylamino)-3-(methylthio)propan-1-ol (10b): An experimental procedure identical to that used for the preparation of **10a** was applied using compound **9b** (229 mg, 1.9 mmol), methanol (5 mL), benzaldehyde (0.24 mL, 2 mmol) and $NaBH_4$ (158 mg, 4 mmol). Product **10b** was obtained as an oil in a yield of 96% (386 mg). IR (film): $\tilde{\nu}$ = 2915, 2866, 1494, 1453, 1436, 1114, 1046, 971, 742, 699. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.24 (m, 5 H), 3.84 (d, *J* = 13.17 Hz, 1 H), 3.76 (d, *J* = 13.17 Hz, 1 H), 3.67 (dd, *J* = 10.98, 3.93 Hz, 1 H), 3.41 (dd, *J* = 10.89, 4.57 Hz, 1 H), 2.84 (m, 1 H), 2.65 (d, *J* = 6.59 Hz, 2 H), 2.00 (s, 3 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.68, 128.38, 127.97, 127.40, 127.05, 126.80, 65.16, 62.32, 55.88, 51.04, 36.47, 15.72 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{11}H_{18}NOS$ 212.1101 $[M + H]^+$; found 212.1103. $[\alpha]_D^{25}$ = −41.36 (*c* = 0.360, $CHCl_3$).

(4*R*)-3-Benzyl-2,2-dimethyl-4-[(methylthio)methyl]oxazolidine (12): A solution of the amino alcohol **10b** (1.0 g, 4.74 mmol) and *p*-toluenesulfonic acid monohydrate (120 mg, 0.6 mmol) in 2,2 dimethoxypropane (11.7 mL, 96 mmol) was heated at reflux for 3 h. The solvent was removed in vacuo, the residue dissolved in ethyl acetate and washed with $NaHCO_3$ (2 × 20 mL). The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo. The crude product was purified by column chromatography (silica, ethyl acetate/hexane, 1:9) to afford 41% (483 mg) of **12** as an oil. IR (film): $\tilde{\nu}$ = 2989, 2916, 2827, 1462, 1454, 1379, 1368, 1212, 1183, 1151, 1084, 1078, 850, 734, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36−7.23 (m, 5 H), 3.88 (dd, *J* = 16.60, 13.42 Hz, 1 H), 3.85 (dd, *J* = 16.60, 13.30 Hz, 1 H), 3.48 (m, 2 H), 2.87 (m, 1 H), 2.69 (dd, *J* = 13.43, 5.98 Hz, 1 H), 2.60 (dd, *J* = 13.43, 6.72 Hz, 1 H), 2.03 (s, 3 H), 1.33 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 140.17, 128.19, 127.9, 126.73, 126.69, 99.86, 62.03, 55.38, 51.45, 36.70, 24.42, 15.97 ppm. HRMS-ESI: *m*/*z* calcd. for $C_{14}H_{22}NOS$ 252.1415 $[M + H]^+$; found 252.1426. $[\alpha]_D^{25}$ = −25.04 (*c* = 0.366, $CHCl_3$).

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