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On the influence of chiral auxiliaries in the stereoselective cross-coupling reactions of titanium enolates and acetals

Jessica Baiget, Annabel Cosp, Erik Gálvez, Loreto Gómez-Pinal, Pedro Romea *, Fèlix Urpí *

Departament de Química Orgànica, Universitat de Barcelona, Martí i Franqués 1–11, 08028 Barcelona, Catalonia, Spain

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ABSTRACT

Titanium enolates from chiral *N*-propanoyl-1,3-thiazolidine-2-thiones containing bulky substituents at C4 turned out to be excellent platforms to get highly stereocontrolled cross-coupling reactions with acetals. Related oxazolidinethiones also afforded good results, but the corresponding oxazolidinones resulted completely unselective for such reactions, which proves that an exocyclic C=S bond is essential to attain a synthetically useful stereocontrol.

1. Introduction

It is beyond all doubt that chiral auxiliaries have been greatly responsible for the amazing development of highly stereoselective methodologies occurred throughout the last decades, which have made possible the construction of structurally complex molecular architectures that were considered unattainable few years ago.[1] Even in our days, when the state of the art in the asymmetric synthesis arena is currently associated to the accomplishments on catalysis, chiral auxiliary-based processes still maintain a prominent position among the most reliable strategies for accessing a single stereoisomer in high yields.[2] Moreover, a thorough and endless analysis of the influence of the structural features of many chiral auxiliaries on the stereochemical outcome of the processes in which they are involved has provided a better understanding of their reactivity and improved their synthetic efficiency.[2]

That is the case for oxazolidinones, probably the most representative family of chiral auxiliaries.[3] Indeed, chiral 1,3-oxazolidinones, first introduced by Evans,[4] have turned out to be a superb tool for the stereoselective construction of carbon–carbon bonds and have enjoyed tremendous success.[5] Nevertheless, the diastereoselectivity imparted by these auxiliaries is occasionally low, as for the acetate-like aldol reaction.[4,6] Interestingly, Nagao and Fujita recognized that tin(II) enolate from analogous *N*-acetyl-1,3-thiazolidine-2-thiones could participate in highly stereoselective aldol processes.[7] Further contributions have shown that other thiazolidinethiones also impart excellent levels of stereocontrol provided that a bulky substituent is incorporated to the heterocycle.[8] On the whole, it has been established that a sulfur atom at the exocyclic position offers different modes of metal binding for enolates and gives access to alternative stereoisomers. Thus, chiral 1,3-thiazolidine- and 1,3-oxazolidine-2-thiones represented in Figure 1 have emerged as suitable platforms to attain highly stereoselective carbon–carbon bond formation reactions.[7–10]

In this context, we have disclosed a straightforward entry to enantiopure *anti* β-alkoxy-α-methyl oxygenated derivatives based on the Lewis acid-mediated addition of titanium enolates from (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione to aliphatic, aromatic, and α,β-unsaturated acetals and the easy removal of the chiral auxiliary (Scheme 1).[11]

Once established the synthetic potential of this new methodology, two structural issues remained still unclear: the influence of (i)

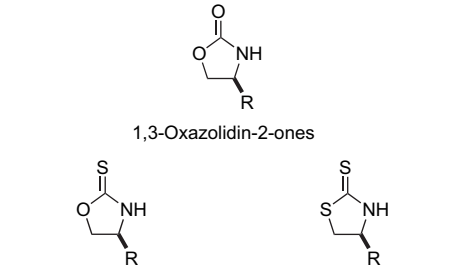

Figure 1.

* Corresponding authors. Tel.: +34 93 4021247/4039106; fax: +34 93 3397878 (F.U.).
E-mail addresses: pedro.romea@ub.edu (P. Romea), felix.urpi@ub.edu (F. Urpí).

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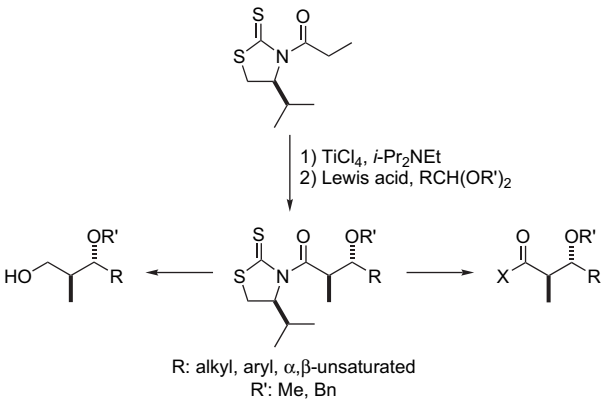
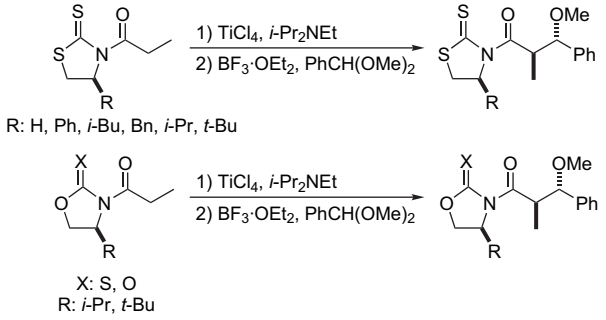


Scheme 1.



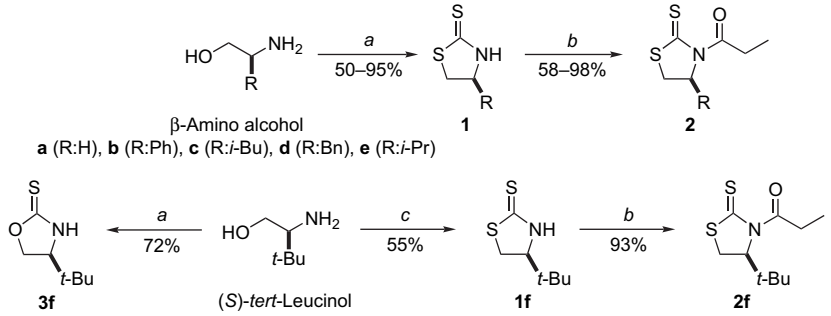
Scheme 2.

different 1,3-thiazolidine-2-thiones and (ii) related chiral auxiliaries on the stereochemical outcome of the process. Herein, we document the impact of different substituents R positioned at C4 in *N*-propanoyl-1,3-thiazolidine-2-thiones on the addition of their titanium enolates to a representative acetal, namely the dimethyl acetal of benzaldehyde (see Scheme 2). Additionally, these studies have been expanded to related 1,3-oxazolidine-2-thione and 1,3-oxazolidin-2-one chiral auxiliaries (see Scheme 2).

2. Results and discussion

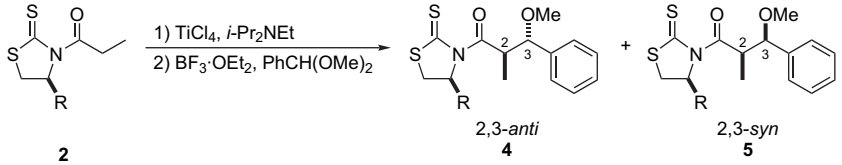
At first, we were concerned with the stereochemical control imparted by the 1,3-thiazolidine-2-thiones **1** shown in Scheme 3. With the exception of **1f** (R: *t*-Bu), these sulfur-containing heterocycles were easily prepared by refluxing an alkaline solution (2.25 M KOH in 1:1 EtOH/H_2O) of the corresponding β-amino alcohol and carbon disulfide for three days.[12] In turn, the thiazolidinethione **1f** derived from the (*S*)-*tert*-leucinol required harsher conditions (5 M KOH in H_2O) due to the steric hindrance imposed by the bulky *tert*-butyl group (Scheme 3).[8b] As a rule, such stringent conditions are needed to overcome the formation of the related 1,3-oxazolidine-2-thiones and to obtain the 1,3-thiazolidine-2-thiones **1** as a sole product, usually pure enough to be used in the next step without any chromatographic purification. Thus, such experimental procedure turns out to be particularly useful to prepare the chiral auxiliaries **1** in multigram scale. Eventually, their acylation with propanoyl chloride proceeded smoothly to afford the desired *N*-propanoyl-1,3-thiazolidine-2-thiones **2** in high yields.

With a reliable supply of a wide set of *N*-propanoyl-1,3-thiazolidine-2-thiones **2**, we began to study the addition of their titanium enolates to the dimethyl acetal of benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ under the conditions previously optimized.[13] The results are summarized in Table 1.



Scheme 3. Reagents and conditions: (a) CS_2, KOH, EtOH/H_2O 1:1, reflux, 72 h. (b) EtCOCl, BuLi, THF, −78 °C. (c) CS_2, KOH, H_2O, reflux, 72 h.

Table 1



Entry	**2**	R	dr (**4**/**5**)[a]	Yield[b] (%)
1	**a**	H	65:35	40 (61)
2	**b**	Ph	76:24	64 (86)
3	**c**	*i*-Bu	76:24	(88)
4	**d**	Bn	85:15	(73)
5	**e**	*i*-Pr	88:12	75 (87)
6	**f**	*t*-Bu	90:10	(57)

[a] Determined by HPLC.
[b] Isolated yield of the 2,3-*anti* diastereomer **4**; values in brackets denote overall yield.

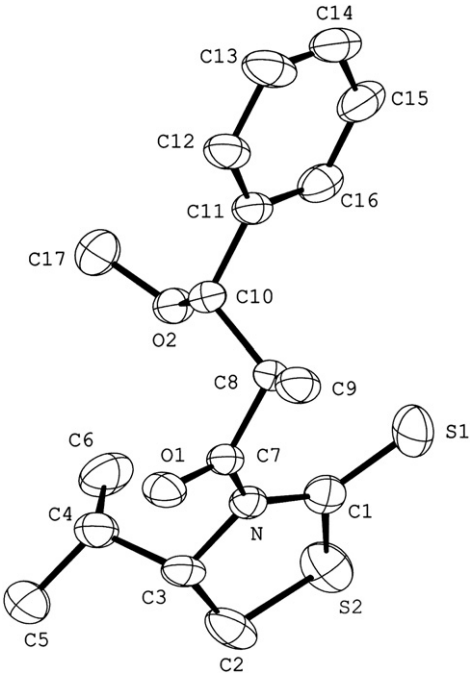
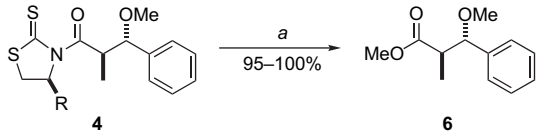


Figure 2.

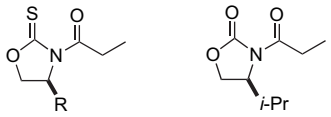
The absolute configuration of the 2,3-*anti* adduct **4e** was firmly established through X-ray analysis (Fig. 2).[14] Other 2,3-*anti* relationships on major diastereomers **4** were secured by removal of the chiral auxiliaries with methanol and comparison of the resultant methyl esters **6** (Scheme 4). Furthermore, the $^3J_{2,3}$ coupling constants of **4** ($^3J_{2,3}$ 9.8–9.9 Hz, see Section 3) and **5** ($^3J_{2,3}$ 6.6–7.0 Hz) resulted to be independent of the C4 substituent and were used as a diagnostic tool to assign the relative configuration of the adducts **4** and **5**.[15]



4 **6**

Scheme 4. Reagents and conditions: (a) MeOH, K_2CO_3, rt.

As shown in Table 1, the diastereoselectivity achieved in such cross-coupling reactions depends on the heterocycles **1**. The most simple *N*-propanoyl-1,3-thiazolidine-2-thione (R: H) **2a** affords the 2,3-*anti* adduct **4a** in a moderate selectivity (dr 65:35), which is improved by all the other C4 substituted chiral auxiliaries. In fact, the diastereoselectivity increases with steric bulk of R (compare entries 1 and 2–6 in Table 1)[16] to reach the best figures with **2e** (R: *i*-Pr) and **2f** (R: *t*-Bu), respectively (see entries 5 and 6 in Table 1). From practical purposes, the valine-derived auxiliary **1e** might be the most reasonable choice because the stereochemical control achieved by **2e** and **2f** is very close (dr 88:12 vs 90:10) being much better than the yield for **2e** (87 vs 57%, see entries 5 and 6 in Table 1).[17,18]



7e R: *i*-Pr
7f R: *t*-Bu

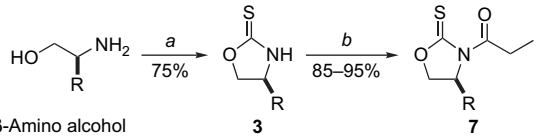
8e

Figure 3.

Importantly, only two of four possible diastereomers, namely 2,3-*anti* **4** and 2,3-*syn* **5** adducts, are observed across all the reaction mixtures. Therefore, it occurs as the substituent positioned at C4 in **2** prevents the addition of the electrophile to the *Re* face of the enolate and is responsible for the *R* configuration of the α-stereocenter in **4** and **5**. This and other evidences suggest that the addition proceeds through a S_N1-like mechanism that involves the formation of an oxonium cation.[19–21] Then, such oxonium cation reacts with the less sterically hindered face of a chelated enolate following an antiperiplanar approach in an open transition state (Scheme 5). This mechanistic picture would be common for all the *N*-propanoyl-1,3-thiazolidine-2-thiones **2**. Regarding the influence of R on the configuration of the β-stereocenter, we are aware that this model does not account easily for the differences on diastereoselectivity. We just speculate that the improvement of diastereomeric ratios achieved from achiral **2a** to the more bulky **2f** might be due to subtle changes on the structure of the enolate produced by the substituent positioned at C4.[22]

Having disclosed the influence of **2** on the stereochemical outcome of the Lewis acid-mediated addition of their titanium enolates to $PhCH(OMe)_2$, we next evaluated the behavior of *N*-propanoyl 1,3-oxazolidine-2-thiones **7** and 1,3-oxazolidin-2-one **8e** containing isopropyl and *tert*-butyl groups at C4 (Fig. 3).

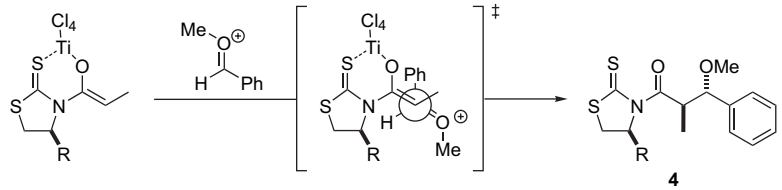
The *N*-propanoyl 1,3-oxazolidin-2-thiones **7** were prepared in good yields by acylation with propanoyl chloride of the chiral 1,3-oxazolidin-2-thiones **3**, which, in turn, were obtained from the corresponding amino alcohols (Scheme 6). As represented in Scheme 3, (*S*)-4-*tert*-butyl-1,3-oxazolidine-2-thione (**3f**) was unexpectedly obtained when (*S*)-*tert*-leucinol was treated with carbon disulfide in a strong basic solution for a long time. Conversely, the less bulky (*S*)-4-isopropyl-1,3-oxazolidine-2-thione (**3e**) required milder experimental conditions and was isolated in good yield by simple stirring at room temperature in the presence of a weak base as triethylamine. Otherwise, standard acylation of the commercially available (*S*)-4-isopropyl-1,3-oxazolidin-2-one with propanoyl chloride delivered the desired (*S*)-4-isopropyl-*N*-propanoyl-1,3-oxazolidin-2-one (**8e**) in 81% yield.



β-Amino alcohol
e (R: *i*-Pr), **f** (R: *t*-Bu)

3 **7**

Scheme 6. Reagents and conditions: (a) CS_2, Et_3N, THF, reflux, 12 h [for R: *t*-Bu, see Scheme 3]. (b) EtCOCl, BuLi, THF, −78 °C.

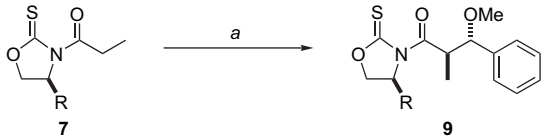


4

Scheme 5.

Unfortunately, the *N*-acyl oxazolidinone **8e** proved to be stereochemically unselective in the cross-coupling reaction with the dimethyl acetal of benzaldehyde. Indeed, the addition of the titanium enolate from **8e** to $PhCH(OMe)_2$ in the presence of a wide array of Lewis acids ($BF_3{\cdot}OEt_2$, BCl_3, $SnCl_4$, $TiCl_4$, etc.) proceeded smoothly and delivered the corresponding adducts in good yields but in unacceptable low diastereomeric ratios (dr<60:40). Interestingly, only two diastereomers were observed, which proves the absolute control exerted by the isopropyl group positioned at C4 on the configuration of the new α-stereocenter.

Better results were achieved with the *N*-acyl oxazolidinethiones **7** (Fig. 3). As shown in Scheme 7, both (*S*)-4-isopropyl-*N*-propanoyl-1,3-oxazolidine-2-thione (**7e**) and (*S*)-4-*tert*-butyl-*N*-propanoyl-1,3-oxazolidine-2-thione (**7f**) afforded the corresponding adducts in close diastereoselectivity than the related thiazolidinethiones **2e** and **2f**, which proves that the stereochemical control on these cross-coupling reactions is associated to the presence of an exocyclic sulfur atom (C=S).[23] Once again, the most sterically hindered *tert*-leucine derived oxazolidinethione **7f** afforded the 2,3-*anti* adduct **9f** in higher diastereomeric ratio but in modest yield.



Scheme 7. Reagents and conditions: (a) (i) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2. (ii) $BF_3{\cdot}OEt_2$, $PhCH(OMe)_2$.

In conclusion, the stereochemical outcome of the cross-coupling reactions of titanium enolates from C4 substituted *N*-propanoyl-1,3-thiazolidine-2-thiones with $PhCH(OMe)_2$ in the presence of $BF_3{\cdot}OEt_2$ relies on the steric bulk of the C4 substituent, being the valine-derived chiral auxiliary the best choice to obtain the corresponding 2,3-*anti* adduct in high yield and diastereomeric ratio. Related 1,3-oxazolidine-2-thiones afford similar results but in poorer yield and diastereoselectivity. Furthermore, the valine-derived 1,3-oxazolidin-2-one resulted useless for such reactions. Thus, the presence of a sulfur atom in the exocyclic double bond is essential to attain a synthetically useful stereocontrol.

3. Experimental

3.1. General

Melting points were taken on an Electrothermal apparatus and are uncorrected. Specific rotations were determined at 20 °C on a Perkin–Elmer 241 MC polarimeter. IR spectra were recorded on a Nicolet 510FT spectrometer and only the more representative frequencies (cm^{-1}) are reported. ^1H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus spectrometer; ^1H NMR (400 MHz) spectra were recorded on a Varian Mercury; chemical shifts (δ) are quoted in parts per million and referenced to internal TMS for ^1H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR; data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; hept, heptuplet; oct, octet; m, multiplet; br, broad; coupling constants (*J*) are quoted in hertz; where appropriate, 2D techniques were also used to assist in structural elucidation. Mass spectra were obtained from the Centro de Apoio Cientifico Tecnoloxico a Investigacion (C.A.C.T.I.), Universidad de Vigo and from the Servei d'Espectrometria de Masses, Universitat de Barcelona. Elemental analyses were obtained from the Servei de Microanàlisi (CID–CSIC, Barcelona). HPLC was carried out with a silica gel Spherisorb S3W (250×4 mm) column with a 0.9 mL min^{-1} flux. Flash chromatography was performed on SDS silica gel (35–70 μm). Analytical thin layer chromatography was carried out on Merck Kieselgel 60 F_{254} plates. The following solvents and reagents were purified and dried according to the standard procedures: CH_2Cl_2, THF, and *i*-Pr_2NEt. All other reagents were used as received.

3.2. General procedure for the preparation of 1,3-thiazolidine-2-thiones (1)

A 2.25 M KOH in 1:1 EtOH/H_2O solution (120 mL) was added dropwise to a solution of enantiomerically pure β-amino alcohol (0.1 mol) and carbon disulfide (18 mL, 0.265 mol) in ethanol (30 mL) at room temperature and under N_2. The reaction mixture was stirred and heated at reflux for 72 h under N_2. After cooling, the volatiles were removed with a rotary evaporator. Then, a 0.5 M aqueous HCl (350 mL) was carefully added at room temperature and the resulting mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed to give the corresponding 1,3-thiazolidine-2-thiones **1** as a solid, which was usually used in the next step without further purification. Otherwise, this material was purified through a short column chromatography to afford purer samples.

3.2.1. 1,3-Thiazolidine-2-thione (*1a*)

Yield: 58%; white solid; R_f 0.20 (CH_2Cl_2); mp 105–106 °C; IR (KBr): 3141, 2849, 1516, 1296, 1051; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.00 (1H, br s, N*H*), 4.04–3.96 (2H, *AA*′BB′X system, NCH_2), 3.61–3.54 (2H, AA′*BB*′X system, SCH_2); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.8, 51.3, 33.6; MS–CI (NH_3): *m*/*z* (%) 120 $[M+H]^+$ (100).

3.2.2. (S)-4-Phenyl-1,3-thiazolidine-2-thione (*1b*)

Yield: 77%; white solid; R_f 0.40 (CH_2Cl_2); mp 124–126 °C [lit.[12a] mp 124–125 °C]; $[\alpha]_D$ −213.5 (*c* 1.1, $CHCl_3$) [lit.[12a] $[\alpha]_D$ −209.3 (*c* 0.35, $CHCl_3$)]; IR (KBr): 3124, 2950, 1492, 1453, 1258, 1050; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.60 (1H, br s, N*H*), 7.50–7.40 (5H, m, Ar*H*), 5.35–5.25 (1H, m, NC*H*), 3.85 (1H, dd, *J*=11.2, 8.0, SCH_xH_y), 3.51 (1H, dd, *J*=11.2, 8.3, SCH_xH_y); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.7, 138.0, 129.3, 129.2, 126.2, 67.3, 41.6; MS–CI (NH_3): *m*/*z* (%) 196 $[M+H]^+$ (100).

3.2.3. (S)-4-Isobutyl-1,3-thiazolidine-2-thione (*1c*)

Yield: 50%; white solid; R_f 0.40 (CH_2Cl_2); mp 48–50 °C; $[\alpha]_D$ −28.8 (*c* 1.0, $CHCl_3$); IR (KBr): 3143, 2957, 2869, 1507, 1467, 1305, 1033; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.06 (1H, br s, N*H*), 4.38–4.26 (1H, m, NC*H*), 3.59 (1H, dd, *J*=11.0, 7.7, SCH_xH_y), 3.22 (1H, dd, *J*=11.0, 7.9, SCH_xH_y), 1.80–1.60 (2H, m, $CH_xH_yCH(CH_3)_2$), 1.55–1.45 (1H, m, $CH_xH_yCH(CH_3)_2$), 0.97 (3H, d, *J*=6.6, CH_3), 0.96 (3H, d, *J*=6.4, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 200.7, 62.5, 42.9, 38.9, 25.3, 22.6, 22.2. Anal. Calcd for $C_7H_{13}NS_2$: C, 47.96; H, 7.47; N, 7.99. Found: C, 47.91; H, 7.50; N, 7.71.

3.2.4. (S)-4-Benzyl-1,3-thiazolidine-2-thione (*1d*)

Yield: 95%; white solid; R_f 0.35 (CH_2Cl_2); mp 74–75 °C [lit.[12a] mp 84–85 °C]; $[\alpha]_D$ −119.2 (*c* 1.0, $CHCl_3$) [lit.[12a] $[\alpha]_D$ −129.2 (*c* 0.96, $CHCl_3$)]; IR (KBr): 3134, 2969, 1509, 1494, 1004; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.45 (1H, br s, N*H*), 7.40–7.26 (3H, m, Ar*H*), 7.23–7.17 (2H, m, Ar*H*), 4.52–4.40 (1H, m, NC*H*), 3.60 (1H, dd, *J*=11.2, 7.7, SCH_xH_y), 3.33 (1H, dd, *J*=11.2, 6.8, SCH_xH_y), 3.03 (1H, dd, *J*=13.6, 7.6, $PhCH_aH_b$), 2.98 (1H, dd, *J*=13.6, 6.7, $PhCH_aH_b$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 200.8, 135.7, 129.0 (×2), 127.4, 65.0, 39.9, 38.0; MS–CI (NH_3): *m*/*z* (%) 210 $[M+H]^+$ (100).

3.2.5. (S)-4-Isopropyl-1,3-thiazolidine-2-thione (*1e*)

Yield: 92%; white solid; R_f 0.25 (CH_2Cl_2); mp 68–69 °C [lit.[7] mp 67–68 °C, lit.[12a] mp 66–67 °C]; $[\alpha]_D$ −34.9 (*c* 1.1, $CHCl_3$) [lit.[7] $[\alpha]_D$

−36.8 (*c* 1.16, $CHCl_3$), lit.[12a] $[\alpha]_D$ −34.6 (*c* 0.94, $CHCl_3$)]; IR (KBr): 3190, 2965, 1500, 1410, 1385, 1030; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42 (1H, br s, N*H*), 4.03 (1H, td, *J*=8.2, 7.8, NC*H*), 3.52 (1H, dd, *J*=11.0, 8.2, SCH_xH$_y$), 3.34 (1H, dd, *J*=11.0, 8.2, SCH$_x$*H*$_y$), 2.10–1.95 (1H, m, C*H*(CH_3)$_2$), 1.04 (3H, d, *J*=7.0, CH_3), 1.01 (3H, d, *J*=7.2, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.5, 70.6, 36.5, 32.5, 19.3, 18.7. Anal. Calcd for $C_6H_{11}NS_2$: C, 44.68; H, 6.87; N, 8.68. Found: C, 44.74; H, 6.81; N, 8.55.

3.3. Preparation of (*S*)-4-*tert*-butyl-1,3-thiazolidine-2-thione (1f)

A mixture of (*S*)-*tert*-leucinol (2.09 g, 17.8 mmol), carbon disulfide (9.2 mL, 150 mmol) in 5 M KOH aqueous solution (100 mL) was heated for 72 h under N_2. The reaction mixture was extracted with CH_2Cl_2 (3×100 mL), the organic layers were dried ($MgSO_4$), and concentrated. The resulting oil was purified by flash chromatography (CH_2Cl_2) to afford 1.74 g (9.9 mmol, 55%) of (*S*)-4-*tert*-butyl-1,3-thiazolidine-2-thione (**1f**). White solid; R_f 0.65 (CH_2Cl_2); mp 134–135 °C [lit.[24] mp 143–144 °C]; $[\alpha]_D$ −35.8 (*c* 1.1, $CHCl_3$) [lit.[24] $[\alpha]_D$ −33.2 (*c* 1.03, $CHCl_3$)]; IR (KBr): 3157, 2958, 1507, 1475, 1368, 1293, 1042; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60 (1H, br s, N*H*), 4.07–3.98 (1H, m, NC*H*), 3.45 (1H, dd, *J*=11.3, 8.4, SCH_xH$_y$), 3.39 (1H, dd, *J*=11.3, 9.0, SCH$_x$*H*$_y$), 1.02 (9H, s, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.6, 73.4, 34.4 (×2), 25.9; HRMS (+ESI): calcd for $[M+H]^+$ $C_7H_{14}NS_2$ 176.0562, found 176.0567.

3.4. General procedure for the acylation of the 1,3-thiazolidine-2-thiones

A 1.5 M solution of *n*-BuLi in hexanes (7.4 mL, 11 mmol) was added dropwise to a solution of 1,3-thiazolidine-2-thione **1** (10 mmol) in THF (6.6 mL) at −78 °C under N_2. The reaction mixture was stirred for 15 min and propanoyl chloride (1.1 mL, 12.5 mmol) was carefully added. The resulting clear solution was stirred for 5 min and the solution was allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was cooled with an ice-water bath and was quenched with a saturated solution of NH_4Cl (4 mL) and water (10 mL). This mixture was extracted with CH_2Cl_2 (3×20 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The resultant oil was purified through column chromatography to afford the corresponding *N*-propanoyl-1,3-thiazolidine-2-thione **2**.

3.4.1. *N-Propanoyl-1,3-thiazolidine-2-thione (**2a**)*

Yield: 58%; bright yellow oil; R_f 0.65 (CH_2Cl_2); IR (film): 2979, 2938, 1702, 1365, 1281, 1222, 1157; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.59 (2H, t, *J*=7.6, NCH_2), 3.28 (2H, t, *J*=7.6, SCH_2), 3.26 (2H, q, *J*=7.3, COCH_2), 1.18 (3H, t, *J*=7.3, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.5, 175.5, 56.0, 32.2, 28.2, 8.7; MS–CI (NH_3): *m*/*z* (%) 176 $[M+H]^+$ (100).

3.4.2. *(S)-4-Phenyl-N-propanoyl-1,3-thiazolidine-2-thione (**2b**)*

Yield: 84%; viscous yellow oil; R_f 0.65 (CH_2Cl_2); $[\alpha]_D$ −301.3 (*c* 1.0, $CHCl_3$); IR (KBr): 2977, 1692, 1320, 1254, 1233, 1164, 1052; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.30 (5H, m, Ar*H*), 6.24 (1H, dd, *J*=8.2, 1.6, NC*H*), 3.93 (1H, dd, *J*=11.3, 8.2, SCH_xH$_y$), 3.38 (1H, dq, *J*=18.1, 7.3, COCH_xH$_y$), 3.20 (1H, dq, *J*=18.1, 7.3, COCH$_x$*H*$_y$), 3.07 (1H, dd, *J*=11.3, 1.6, SCH$_x$*H*$_y$), 1.13 (3H, t, *J*=7.3, COCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 202.1, 174.8, 139.3, 129.0, 128.4, 125.4, 69.8, 36.6, 32.5, 8.7; HRMS (+ESI): calcd for $[M+H]^+$ $C_{12}H_{14}NOS_2$ 252.0511, found 252.0509.

3.4.3. *(S)-4-Isobutyl-N-propanoyl-1,3-thiazolidine-2-thione (**2c**)*

Yield: 81%; bright yellow oil; R_f 0.45 (50:50 CH_2Cl_2/hexanes); $[\alpha]_D$ +269.8 (*c* 1.05, $CHCl_3$); IR (film): 2959, 1701, 1341, 1269, 1161, 1099; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.35–5.20 (1H, m, NC*H*), 3.56 (1H, ddd, *J*=11.2, 7.2, 1.2, SCH_xH$_y$), 3.36 (1H, dq, *J*=18.1, 7.2, COCH_xH$_y$), 3.10 (1H, dq, *J*=18.1, 7.2, COCH$_x$*H*$_y$), 2.91 (1H, dd, *J*=11.2, 0.7, SCH$_x$*H*$_y$), 1.98–1.86 (1H, m, CH_xH$_y$CH(CH_3)$_2$), 1.74–1.48 (2H, m, CH$_x$*H*$_y$C*H*(CH_3)$_2$), 1.17 (3H, t, *J*=7.2, COCH$_2$CH_3), 1.01 (3H, d, *J*=6.4, CHCH_3), 1.00 (3H, d, *J*=6.4, CHCH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.4, 174.7, 66.1, 39.6, 33.0, 32.2, 25.4, 23.5, 21.2, 8.8; HRMS (+ESI): calcd for $[M+H]^+$ $C_{10}H_{18}NOS_2$ 232.0824, found 232.0828.

3.4.4. *(S)-4-Benzyl-N-propanoyl-1,3-thiazolidine-2-thione (**2d**)*

Yield: 89%; yellow solid; R_f 0.40 (50:50 CH_2Cl_2/hexanes); mp 95–97 °C; $[\alpha]_D$ +196.4 (*c* 1.1, $CHCl_3$); IR (KBr): 2977, 1706, 1264, 1165, 1032; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.26 (5H, m, Ar*H*), 5.42–5.35 (1H, m, NC*H*), 3.42 (1H, dq, *J*=18.2, 7.2, COCH_xH$_y$), 3.38 (1H, ddd, *J*=11.5, 7.2, 1.2, SCH_xH$_y$), 3.22 (1H, dd, *J*=13.1, 3.8, PhCH_xH$_y$), 3.13 (1H, dq, *J*=18.2, 7.2, COCH$_x$*H*$_y$), 3.05 (1H, dd, *J*=13.1, 10.5, PhCH$_x$*H*$_y$), 2.88 (1H, dd, *J*=11.5, 0.7, SCH$_x$*H*$_y$), 1.19 (3H, t, *J*=7.2, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.1, 174.9, 136.6, 129.4, 128.9, 127.2, 68.6, 36.7, 32.3, 31.9, 8.8. Anal. Calcd for $C_{13}H_{15}NOS_2$: C, 58.83; H, 5.70; N, 5.28. Found: C, 58.67; H, 5.62; N, 5.22.

3.4.5. *(S)-4-Isopropyl-N-propanoyl-1,3-thiazolidine-2-thione (**2e**)*

Yield: 98%; bright yellow oil; R_f 0.45 (50:50 CH_2Cl_2/hexanes); $[\alpha]_D$ +428.5 (*c* 1.0, $CHCl_3$); IR (film): 2961, 1699, 1349, 1259, 1167; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.17 (1H, ddd, *J*=8.1, 6.1, 1.2, NC*H*), 3.51 (1H, dd, *J*=11.4, 8.1, SCH_xH$_y$), 3.36 (1H, dq, *J*=18.0, 7.2, COCH_xH$_y$), 3.15 (1H, dq, *J*=18.0, 7.2, COCH$_x$*H*$_y$), 3.02 (1H, dd, *J*=11.4, 1.2, SCH$_x$*H*$_y$), 2.41–2.32 (1H, m, C*H*(CH_3)$_2$), 1.15 (3H, t, *J*=7.2, COCH$_2$CH_3), 1.06 (3H, d, *J*=6.6, CH_3CCH$_3$), 0.98 (3H, d, *J*=6.6, CH$_3$CCH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 203.3, 174.8, 71.6, 32.0, 30.8, 30.4, 19.0, 17.6, 8.9. Anal. Calcd for $C_9H_{15}NOS_2$: C, 49.73; H, 6.96; N, 6.44. Found: C, 49.67; H, 6.94; N, 6.36.

3.4.6. *(S)-4-tert-Butyl-N-propanoyl-1,3-thiazolidine-2-thione (**2f**)*

Yield: 93%; yellow solid; R_f 0.50 (50:50 CH_2Cl_2/hexanes); mp 29–30 °C; $[\alpha]_D$ +602.4 (*c* 0.85, $CHCl_3$); IR (KBr): 2964, 1703, 1353, 1325, 1250, 1156, 1045; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.35 (1H, dd, *J*=8.4, 0.7, NC*H*), 3.54 (1H, dd, *J*=11.4, 8.4, SCH_xH$_y$), 3.36 (1H, dq, *J*=17.9, 7.2, COCH_xH$_y$), 3.21 (1H, dq, *J*=17.9, 7.2, COCH$_x$*H*$_y$), 3.10 (1H, dd, *J*=11.4, 0.7, SCH$_x$*H*$_y$), 1.18 (3H, t, *J*=7.2, COCH$_2$CH_3), 1.03 (9H, s, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 204.7, 174.5, 72.4, 37.9, 31.8, 30.5, 26.8, 9.2.

3.5. General procedure for the titanium-mediated addition of 2 to PhCH(OMe)$_2$

Neat $TiCl_4$ (0.12 mL, 1.1 mmol) was added dropwise to a solution of **2** (1.0 mmol) in anhydrous CH_2Cl_2 (8 mL), at 0 °C under N_2. The yellow suspension was stirred for 5 min at 0 °C, cooled at −78 °C, and a solution of anhydrous diisopropylethylamine (0.19 mL, 1.1 mmol) in anhydrous CH_2Cl_2 (1 mL) was added. The dark red enolate solution was stirred for 2 h at −40 °C and cooled at −78 °C. Then, $BF_3{\cdot}OEt_2$ (140 μL, 1.1 mmol) and PhCH(OMe)$_2$ (166 μL, 1.1 mmol) were successively added dropwise. The resulting mixture was stirred at −78 °C for 2.5 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl (6 mL) with vigorous stirring and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2 (10 mL), and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was analyzed by HPLC and purified through flash column chromatography with deactivated silica gel (2.5% Et_3N) to afford the 2,3-*anti* adduct **4** as a pure diastereomer or as a mixture with the 2,3-*syn* adduct **5**. Eventually, the product was kept in the fridge under nitrogen atmosphere to avoid undesired decompositions.

*3.5.1. (±) N-[2,3-anti-3-Methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**4a**)*

Yield: 40%; yellow solid; R_f 0.70 (CH_2Cl_2); mp 132–133 °C; IR (KBr): 2981, 2934, 1700, 1364, 1278, 1153; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.28 (5H, m, Ar*H*), 4.72–4.60 (2H, m, COC*H*CH$_3$, NCH$_x$H$_y$), 4.46 (1H, ddd, *J*=11.9, 11.1, 7.6, NCH$_x$*H*$_y$), 4.33 (1H, d, *J*=9.8, C*H*OCH$_3$), 3.43 (1H, td, *J*=11.1, 7.8, SC*H*$_x$H$_y$), 3.21 (1H, ddd, *J*=11.1, 7.6, 3.2, SCH$_x$*H*$_y$), 3.11 (3H, s, OC*H*$_3$), 0.95 (3H, d, *J*=6.7, COCHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.6, 178.6, 138.8, 128.5, 128.3, 127.9, 87.6, 56.8, 56.5, 46.2, 28.9, 14.1; MS–CI (NH_3): *m*/*z* (%) 264 [M−OMe]$^+$ (60), 296 [M+H]$^+$ (100).

*3.5.2. (S)-N-[(2R,3S)-3-Methoxy-2-methyl-3-phenylpropanoyl]-4-phenyl-1,3-thiazolidine-2-thione (**4b**)*

Yield: 64%; bright yellow oil; R_f 0.55 (CH_2Cl_2); [α]$_D$ −175.0 (*c* 1.0, $CHCl_3$); HPLC (98:2 hexanes/EtOAc) t_R 54.6 min [2,3-*syn* diastereomer, t_R 38.0 min]; IR (film): 2931, 1702, 1457, 1302, 1254, 1150, 1025; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.50–7.20 (10H, m, Ar*H*), 6.34 (1H, dd, *J*=8.2, 3.3, NC*H*), 5.08 (1H, dq, *J*=9.8, 6.9, COC*H*CH$_3$), 4.19 (1H, d, *J*=9.8, C*H*OCH$_3$), 3.84 (1H, dd, *J*=11.2, 8.2, SC*H*$_x$H$_y$), 3.14 (1H, dd, *J*=11.2, 3.3, SCH$_x$*H*$_y$), 2.87 (3H, s, OC*H*$_3$), 0.85 (3H, d, *J*=6.9, COCHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 202.3, 177.3, 139.0, 138.9, 128.7, 128.4, 128.2 (×2), 128.0, 126.0, 87.7, 70.3, 56.5, 45.5, 36.2, 14.4.

*3.5.3. (S)-4-Isobutyl-N-[(2R,3S)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**4c**)*

Yield of the mixture: 88%; yellow viscous oil; R_f 0.60 (CH_2Cl_2); HPLC (97:3 hexanes/EtOAc) t_R 13.4 min [2,3-*syn* diastereomer, t_R 14.5 min]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.20 (5H, m, Ar*H*), 5.45–5.35 (1H, m, NC*H*), 5.08 (1H, dq, *J*=9.9, 7.0, COC*H*CH$_3$), 4.36 (1H, d, *J*=9.9, C*H*OCH$_3$), 3.53 (1H, ddd, *J*=11.1, 7.6, 0.7, SC*H*$_x$H$_y$), 3.10 (3H, s, OC*H*$_3$), 2.93 (1H, dd, *J*=11.1, 2.6, SCH$_x$*H*$_y$), 2.00–1.60 (3H, m, C*H*$_2$C*H*(CH$_3$)$_2$), 1.02 (3H, d, *J*=6.2, C*H*$_3$), 1.01 (3H, d, *J*=6.4, C*H*$_3$), 0.88 (3H, d, *J*=7.0, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.5, 177.9, 139.0, 128.4, 128.2, 128.0, 87.7, 66.5, 56.5, 45.5, 40.7, 33.0, 25.3, 23.6, 21.3, 14.4.

*3.5.4. (S)-4-Benzyl-N-[(2R,3S)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**4d**)*

Yield of the mixture: 73%. A small amount of pure **4d** was isolated and characterized. Bright yellow oil; R_f 0.17 (70:30 hexanes/CH_2Cl_2); HPLC (99:1 hexanes/EtOAc) t_R 36.6 min [2,3-*syn* diastereomer, t_R 46.2 min]; [α]$_D$ −41.2 (*c* 1.05 in $CHCl_3$); IR (film): 2932, 1697, 1454, 1344, 1252, 1160, 1097; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.25 (10H, m, Ar*H*), 5.60–5.45 (1H, m, NC*H*), 5.22 (1H, dq, *J*=9.8, 6.9, COC*H*CH$_3$), 4.42 (1H, d, *J*=9.8, C*H*OCH$_3$), 3.40–3.25 (2H, m, PhC*H*$_x$H$_y$ and SC*H*$_x$H$_y$), 3.12 (3H, s, OC*H*$_3$), 3.08 (1H, dd, *J*=13.4, 10.5, PhCH$_x$*H*$_y$), 2.90 (1H, dd, *J*=11.4, 2.0, SCH$_x$*H*$_y$), 0.91 (3H, d, *J*=6.9, COCHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 201.4, 177.8, 139.0, 136.8, 129.4, 128.9, 128.5, 128.3, 128.1, 127.2, 87.6, 68.9, 56.7, 45.4, 37.4, 31.5, 14.5; HRMS (+ESI): calcd for [M−OMe]$^+$ $C_{20}H_{20}NOS_2$ 354.0980, found 354.0964; calcd for [M+H]$^+$ $C_{21}H_{24}NO_2S_2$ 386.1242, found 386.1233.

*3.5.5. (S)-4-Isopropyl-N-[(2R,3S)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**4e**)*

Yield: 75%; yellow solid; mp 82–83 °C; R_f 0.60 (CH_2Cl_2); HPLC (97:3 hexanes/EtOAc) t_R 17.1 min [2,3-*syn* diastereomer, t_R 38.0 min]; [α]$_D$ +120.2 (*c* 1.96 in $CHCl_3$); IR (KBr): 2927, 1704, 1368, 1245, 1156; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.22 (5H, m, Ar*H*), 5.36 (1H, ddd, *J*=8.9, 5.5, 2.1, NC*H*), 5.26 (1H, dq, *J*=9.8, 7.0, COC*H*CH$_3$), 4.35 (1H, d, *J*=9.8, C*H*OCH$_3$), 3.46 (1H, dd, *J*=11.5, 8.9, SC*H*$_x$H$_y$), 3.08 (3H, s, OC*H*$_3$), 3.01 (1H, dd, *J*=11.5, 2.1, SCH$_x$*H*$_y$), 2.40 (1H, heptd, *J*=8.0, 5.5, C*H*(CH$_3$)$_2$), 1.11 (3H, d, *J*=8.0, C*H*$_3$CHCH$_3$), 1.03 (3H, d, *J*=8.0, CH$_3$CHC*H*$_3$), 0.86 (3H, d, *J*=7.0, COCHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 202.6, 177.7, 139.1, 128.3, 128.2, 128.1, 87.7, 71.9, 56.4, 45.1, 30.4, 28.8, 19.0, 17.0, 14.3; HRMS (+FAB): calcd for [M+H]$^+$ $C_{17}H_{24}NO_2S_2$ 338.1249, found 338.1251.

*3.5.6. (S)-4-tert-Butyl-N-[(2R,3S)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-thiazolidine-2-thione (**4f**)*

Yield of the mixture: 57%; bright yellow oil; R_f 0.40 (95:5 hexanes/EtOAc); HPLC (99:1 hexanes/EtOAc) t_R 41.4 min [2,3-*syn* diastereomer, t_R 37.1 min]; IR (film): 2965, 1698, 1454, 1370, 1242, 1134; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.29 (5H, m, Ar*H*), 5.53 (1H, dd, *J*=8.5, 0.9, NC*H*), 5.42 (1H, dq, *J*=10.0, 6.9, COC*H*CH$_3$), 4.37 (1H, d, *J*=10.0, C*H*OCH$_3$), 3.49 (1H, dd, *J*=11.7, 8.5, SC*H*$_x$H$_y$), 3.09 (3H, s, OC*H*$_3$), 3.07 (1H, dd, *J*=11.7, 0.9, SCH$_x$*H*$_y$), 1.10 (9H, s, C(C*H*$_3$)$_3$), 0.80 (3H, d, *J*=6.9, COCHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 205.0, 176.3, 139.3, 128.4, 128.2, 128.1, 87.2, 72.5, 56.5, 44.1, 37.9, 29.5, 26.7, 14.3; HRMS (+ESI): calcd for [M–OMe]$^+$ $C_{17}H_{22}NOS_2$ 320.1137, found 320.1149; calcd for [M+H]$^+$ $C_{18}H_{26}NO_2S_2$ 352.1399, found 352.1408.

3.6. General procedure for the removal of chiral auxiliaries: obtention of methyl ester 6

A solution of **4** (0.15 mmol) in anhydrous MeOH (3 mL) was treated with anhydrous K_2CO_3 (104 mg, 0.75 mmol) at 0 °C under N_2. The resultant mixture was stirred at room temperature. The bright yellow color faded slowly and, finally, a control TLC proved that the starting material had been consumed (3–4 h). The reaction was quenched by addition of a saturated solution of NH_4Cl (5 mL) and the resulting suspension was diluted with CH_2Cl_2 (15 mL). The organic layer was washed with a 0.5 M NaOH aqueous solution (5 mL), and water (5 mL), and dried (Na_2SO_4). Removal of the volatiles afforded a colorless oil, which was purified through a short pad of silica when required. Yield: 95–100%; colorless oil; R_f 0.30 (CH_2Cl_2); [α]$_D$ −73.0 (*c* 1.5, $CHCl_3$); IR (film): 2958, 1740, 1459, 1268, 1167, 1098; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.30 (5H, m, Ar*H*), 4.25 (1H, d, *J*=9.8, C*H*OCH$_3$), 3.76 (3H, s, COOC*H*$_3$), 3.15 (3H, s, CHOC*H*$_3$), 2.77 (1H, dq, *J*=9.8, 7.0, COC*H*CH$_3$), 0.87 (1H, d, *J*=7.0, COCHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 175.8, 138.8, 128.4, 128.2, 127.6, 85.8, 56.7, 51.7, 46.9, 14.0; MS–CI (NH_3): *m*/*z* (%) 209 (35) [M+H]$^+$, 226 (100) [M+NH$_4$]$^+$; HRMS (+ESI): calcd for [M−OMe]$^+$ $C_{11}H_{13}O_2$ 177.0910, found 177.0904; calcd for [M+H]$^+$ $C_{12}H_{17}O_3$ 209.1172, found 209.1167.

3.7. Preparation of (*S*)-4-isopropyl-1,3-oxazolidine-2-thione (3e)

Anhydrous triethylamine (5.4 mL, 38.7 mmol) was added dropwise to a solution of (*S*)-valinol (1.01 g, 9.8 mmol) and carbon disulfide (3.0 mL, 50.0 mmol) in anhydrous THF (40 mL) at 0 °C under N_2 and the resultant mixture was heated at reflux for 12 h under N_2. After cooling, the volatiles were removed with a rotary evaporator and the mixture was partitioned with CH_2Cl_2 (150 mL) and water (50 mL). The aqueous layer was further extracted with CH_2Cl_2 (3×100 mL), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The resultant brown residue was purified through a column chromatography (CH_2Cl_2) to afford 1.07 g (7.4 mmol, 75% yield) of (*S*)-4-isopropyl-1,3-oxazolidine-2-thione (**3e**). White solid; mp 49–50 °C [lit.[12a] mp 45–46 °C]; R_f 0.20 (CH_2Cl_2); [α]$_D$ −27.4 (*c* 0.65, $CHCl_3$) [lit.[12a] [α]$_D$ −21.4 (*c* 0.4, $CHCl_3$)]; IR (KBr): 3191, 2964, 1526, 1274, 1171; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.46 (1H, br s, N*H*), 4.69 (1H, t, *J*=9.1, OC*H*$_x$H$_y$), 4.39 (1H, dd, *J*=9.1, 6.7, OCH$_x$*H*$_y$), 3.86 (1H, dt, *J*=9.1, 6.7, NC*H*), 1.84 (1H, oct, *J*=6.7, C*H*(CH$_3$)$_2$), 0.99 (3H, d, *J*=6.7, C*H*$_3$), 0.94 (3H, d, *J*=6.7, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 189.5, 73.4, 62.4, 32.1, 17.9, 17.8; MS–CI (NH_3): *m*/*z* (%) 146 (100) [M+H]$^+$.

3.8. Preparation of (*S*)-4-*tert*-butyl-1,3-oxazolidine-2-thione (3f)

A 2.5 M KOH in 1:1 EtOH/H_2O solution (15 mL) was added dropwise to a solution of (*S*)-*tert*-leucinol (2.52 g, 21.5 mmol) and

carbon disulfide (3.9 mL, 65 mmol) in ethanol (5 mL) at room temperature under N_2 and the reaction mixture was stirred and heated at reflux for 72 h under N_2. After cooling, the volatiles were removed with a rotary evaporator. Then, a 2 M aqueous HCl (350 mL) was carefully added at room temperature until pH 2 and the resulting mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent was removed. The resulting white solid was purified by flash chromatography (CH_2Cl_2) to afford 0.32 g (1.8 mmol, 8%) of **1f** and 2.46 g (15.4 mmol, 72%) of (*S*)-4-*tert*-butyl-1,3-oxazolidine-2-thione (**3f**). White solid; mp 146–149 °C [lit.[24] mp 153–156 °C]; R_f 0.35 (CH_2Cl_2); $[\alpha]_D$ −8.4 (*c* 1.0, $CHCl_3$) [lit.[24] $[\alpha]_D$ −11.8 (*c* 0.98, $CHCl_3$)]; IR (KBr): 3184, 2960, 1534, 1285, 1183; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.40 (1H, br s, N*H*), 4.62 (1H, t, *J*=9.6, OCH_xH$_y$), 4.46 (1H, dd, *J*=9.6, 6.3, OCH$_x$*H*$_y$), 3.81 (1H, dd, *J*=9.6, 6.3, NC*H*), 0.94 (9H, s, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 189.6, 71.8, 65.8, 33.6, 25.0; MS–CI (NH_3): *m*/*z* (%) 160 (100) $[M+H]^+$.

3.9. Acylation of the 1,3-oxazolidine-2-thiones

The acylation of oxazolidinethiones **3** was carried out following the experimental procedure reported for the thiazolidinethiones **1**.

*3.9.1. (S)-4-Isopropyl-N-propanoyl-1,3-oxazolidine-2-thione (**7e**)*

Yield: 85%; white solid; mp 42–43 °C [lit.[25] mp 43–44 °C]; R_f 0.65 (CH_2Cl_2); $[\alpha]_D$ +126.6 (*c* 1.05, $CHCl_3$); [lit.[25] $[\alpha]_D$ +140.2 (*c* 1.07, $CHCl_3$)]; IR (KBr): 2968, 1706, 1465, 1405, 1328, 1200; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.79–4.64 (1H, m, NC*H*), 4.42–4.38 (2H, m, OCH_2), 3.41 (1H, dq, *J*=18.1, 7.2, COCH_xH$_y$), 3.27 (1H, dq, *J*=18.1, 7.2, COCH$_x$*H*$_y$), 2.36 (1H, dhept, *J*=6.9, 3.9, C*H*(CH$_3$)$_2$), 1.20 (3H, t, *J*=7.2, COCH$_2$CH_3), 0.95 (3H, d, *J*=6.9, CH_3CHCH$_3$), 0.90 (3H, d, *J*=6.9, CH$_3$CHCH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 186.0, 174.8, 67.5, 63.2, 31.3, 28.9, 18.2, 14.9, 8.5; HRMS (+ESI): calcd for $[M+H]^+$ $C_9H_{16}NO_2S$ 202.0896, found 202.0899.

*3.9.2. (S)-4-tert-Butyl-N-propanoyl-1,3-oxazolidine-2-thione (**7f**)*

Yield: 95%; colorless oil; R_f 0.40 (50:50 hexanes/CH_2Cl_2); $[\alpha]_D$ +152.2 (*c* 1.1, $CHCl_3$); IR (film): 2968, 1708, 1402, 1326, 1179, 1015; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.78 (1H, dd, *J*=7.5, 1.7, NC*H*), 4.45 (1H, dd, *J*=9.5, 1.7, OCH_xH$_y$), 4.34 (1H, dd, *J*=9.5, 7.5, OCH$_x$*H*$_y$), 3.32 (1H, dq, *J*=18.1, 7.2, COCH_xH$_y$), 3.25 (1H, dq, *J*=18.1, 7.2, COCH$_x$*H*$_y$), 1.21 (3H, t, *J*=7.2, COCH$_2$CH_3), 0.94 (9H, s, C(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 187.0, 174.9, 69.2, 65.1, 36.1, 31.1, 25.8, 8.9; HRMS (+ESI): calcd for $[M+H]^+$ $C_{10}H_{18}NO_2S$ 216.1052, found 216.1053.

3.10. General procedure for the titanium-mediated addition of 7 to PhCH(OMe)$_2$

The cross-coupling reaction of *N*-propanoyl-1,3-oxazolidine-2-thiones **7** and PhCH(OMe)$_2$ was carried out according to the experimental procedure described for **2**.

*3.10.1. (S)-4-Isopropyl-N-[(2R,3S)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-oxazolidine-2-thione (**9e**)*

Yield of mixture: 57%; colorless viscous oil; R_f 0.45 (CH_2Cl_2); HPLC (98:2 hexanes/EtOAc) t_R 40.2 min [2,3-*syn* diastereomer, t_R 48.7 min]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40–7.25 (5H, m, Ar*H*), 5.35 (1H, dq, *J*=9.9, 6.9, COC*H*CH$_3$), 4.86 (1H, ddd, *J*=7.7, 4.9, 3.8, NC*H*), 4.45–4.35 (2H, m, OCH_2), 4.33 (3H, d, *J*=9.9, C*H*OCH$_3$), 3.08 (3H, s, OCH_3), 2.37 (1H, heptd, *J*=7.0, 3.8, C*H*(CH$_3$)$_2$), 0.97 (3H, d, *J*=7.0, CH_3), 0.96 (3H, d, *J*=7.0, CH_3), 0.90 (3H, d, *J*=6.9, CH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 185.5, 175.2, 139.2, 128.2, 127.9, 127.8, 84.3, 66.9, 62.5, 56.8, 44.6, 28.6, 18.1, 14.4, 13.2.

*3.10.2. (S)-4-tert-Butyl-N-[(2R,3S)-3-methoxy-2-methyl-3-phenylpropanoyl]-1,3-oxazolidine-2-thione (**9f**)*

Yield: 56%; colorless oil; R_f 0.75 (CH_2Cl_2); HPLC (96:4 hexanes/EtOAc) t_R 26.3 min [2,3-*syn* diastereomer, t_R 30.8 min]; $[\alpha]_D$ +34.4 (*c* 0.4 in $CHCl_3$); IR (film): 2965, 1701, 1456, 1358, 1254, 1174; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.29 (5H, m, Ar*H*), 5.46 (1H, dq, *J*=10.0, 6.9, COC*H*CH$_3$), 4.91 (1H, dd, *J*=7.8, 1.8, NC*H*), 4.45 (1H, dd, *J*=9.5, 1.8, OCH_xH$_y$), 4.36 (3H, d, *J*=10.0, C*H*OCH$_3$), 4.32 (1H, dd, *J*=9.5, 7.8, OCH$_x$*H*$_y$), 3.08 (3H, s, OCH_3), 1.01 (9H, s, C(CH_3)$_3$), 0.84 (3H, d, *J*=6.9, COCHCH_3); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 186.9, 177.4, 139.1, 128.5, 128.3, 128.2, 87.4, 68.6, 65.0, 56.4, 43.8, 36.2, 25.6, 14.3; HRMS (+ESI): calcd for $[M+H]^+$ $C_{18}H_{26}NO_3S$ 336.1627, found 336.1616; calcd for $[M-OMe]^+$ $C_{17}H_{22}NO_2S$ 304.1365, found 304.1355.

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