Direct *anti* Glycolate Aldol Reaction of Protected Chiral *N*-Hydroxyacetyl Thiazolidinethiones with Acetals Catalyzed by a Nickel(II) Complex

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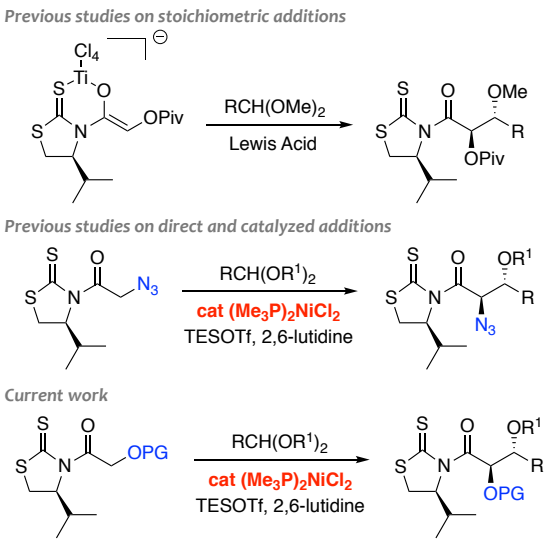
Abstract: The direct and stereocontrolled addition of (*S*)-4-isopropyl-*N*-(2-pivaloyloxyacetyl)-1,3-thiazolidine-2-thione to dialkyl acetals of aromatic and α,β-unsaturated aldehydes catalyzed by 2.5–5 mol% of a nickel(II) complex permits the synthesis of diastereomerically pure and fully protected *anti* aldol adducts in good to high yields. The catalytic species is formed *in situ* from commercially available and easy to handle $(Me_3P)_2NiCl_2$, which makes this reaction a direct, catalytic, and experimentally simple approach to the asymmetric *anti* glycolate aldol reaction.

Introduction

The widespread presence of 1,2,3-trioxygenated arrays in natural products and the synthetic interest for such structural motifs have stimulated the development of a variety of stereoselective and catalytic transformations.[1] Thereby, the enantioselective epoxidation of allylic alcohols and the dihydroxylation of olefins both disclosed by Sharpless are foremost landmarks in asymmetric catalysis and hold a prominent position among all asymmetric procedures.[2] Besides them, Mukaiyama aldol reactions from protected α-hydroxy enol silyl ethers are often used to get stereocontrolled access to the abovementioned trioxygenated structural motifs.[3] Despite the undeniable synthetic potential of these methods, there is a lasting quest for direct, catalytic, and more efficient *constructive* methods.[4] In this context, organocatalysis leads the way and mono- and dihydroxyacetone have become excellent platforms from which to carry out enantioselective aldol reactions under mild conditions.[5] Surprisingly, there is a lack of parallel reactions proceeding through metal enolates that, in principle, might give access to a broader range of trioxygenated motifs.[6] Pioneering studies by Shibasaki established that the direct aldol reaction of hydroxyacetophenone, catalyzed by heterobimetallic and zinc BINOL-derived complexes, afforded *anti* or *syn* glycolate aldol derivatives respectively in high yields with a remarkable stereocontrol.[7] At the same time, Trost reported similar results with zinc ProPhenol catalysts, which produce *syn* glycolate aldol adducts with high yields and enantioselectivities and good diastereomeric ratios.[8,9] Further improvements utilized other aryl α-hydroxymethyl ketones or amides[10] and were applied to the synthesis of natural products,[11] but few significant advances have been reported since then. Interestingly, Shibasaki described a related enantioselective aldol addition of α-sulfanyl 7-azaindolinylamide catalyzed by a copper(I) complex,[12,13] whereas Aoki has recently reported that direct aldol reactions of a protected dihydroxyacetone with aromatic aldehydes catalyzed by zinc complexes containing histidine produce *syn* aldol adducts with good yields and enantioselectivities.[14] In view of the lack of methods to prepare *anti* glycolate adducts and taking advantage of our experience with stoichiometric reactions of titanium(IV) enolates with acetals[15,16] and direct and highly stereoselective carbon-carbon bond forming reactions from chiral *N*-acyl-1,3-thiazolidene-2-thiones catalyzed by nickel(II) complexes,[17,18] we envisaged that Lewis acid-mediated glycolate aldol-like additions to dialkyl acetals might proceed in a highly efficient manner. Importantly, such an approach was supported by the high yields and diastereomeric ratios achieved in the direct addition of *N*-azidoacetyl-4-isopropyl-1,3-thiazolidine-2-thione to dialkyl acetals promoted by 2–5 mol% of $(Me_3P)_2NiCl_2$, a commercially available and easy to handle complex (Scheme 1).[19] Herein, we disclose our results on the direct reaction of protected *N*-hydroxyacetyl-4-isopropyl-1,3-thiazolidine-2-thiones with dialkyl acetals triggered by $(Me_3P)_2NiCl_2$, which produces the corresponding *anti* adducts with good to high yields in a stereocontrolled manner.



Scheme 1. Different approaches to *anti* aldol reactions.

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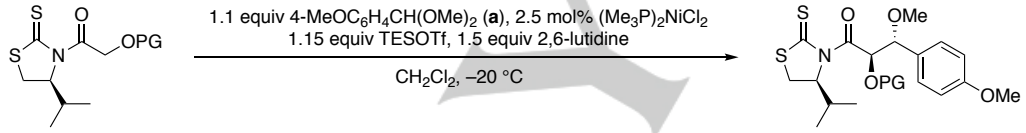
Results and Discussion

Using previously optimized conditions from a related reaction,[19,20] we initially explored the feasibility of the process and the influence of the hydroxyl protecting group on the direct addition of *N*-hydroxyacetyl thiazolidinethiones **1–7** to the dimethyl acetal of 4-methoxybenzaldehyde (**a**). As shown in Table 1, most of the evaluated substrates give good diastereomeric ratios but with variable yields. Concretely, ethers and silyl ether protected hydroxyacetyl thiazolidinethiones **1–5** gave good diastereoselectivities but in moderate or low yields (entries 1–5 in Table 1), whereas those containing ester protecting groups resulted much more favorable (entry 6 and 7 in Table 1). Particularly, the pivaloyl group was chosen as the most suitable protecting group because of the high diastereoselectivity (dr 87:13) and the simplicity of the chromatographic purification, which permitted us to isolate pure *anti* adduct **14a** with a 77% yield by using a tiny 2.5 mol% of $(Me_3P)_2NiCl_2$. Further analyses indicated that reaction times greater than five hours were required (entries 7–9 in Table 1), so the standard time was fixed for 15 h to ensure the completion of any reaction.

The scope of the reaction was first examined with a variety of aromatic dimethyl acetals.[21] The aldol addition proceeded smoothly for activated acetals (**a** and **b** in Table 2) using the abovementioned experimental conditions (2.5 mol% of $(Me_3P)_2NiCl_2$ and 1.15 equivalents of TESOTf). However, it was necessary to increase the $(Me_3P)_2NiCl_2$ loading and the amount of TESOTf to 5 mol% and 2.2 equivalents respectively when less activated acetals (**c–g** in Table 2) were used to achieve adequate yields.[22]

The method was next applied to dialkyl acetals from α,β-unsaturated aldehydes. Addition to 1.1 equivalents of dimethyl acetals from cinnamic aldehydes **h** and **i** afforded the expected *anti* adducts **14h** and **14i** with diastereomeric ratios of 78:22 and 93:7 with yields up to 89% (Table 3). In turn, parallel reactions with less reactive cobalt-substituted propargylic diethyl acetals[23,24] **j** and **k** needed 1.5 equivalents of the electrophile, 5 mol% of $(Me_3P)_2NiCl_2$, and 2.2 equivalents of TESOTf to give the desired adducts **14j** and **14k** with high yields and diastereoselectivities (Table 3).

Table 1. Influence of the hydroxyl protecting group on the addition to the dimethyl acetal of 4-methoxybenzaldehyde (**a**)

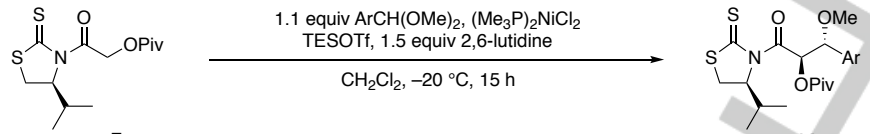


1–7 **8a–14a**

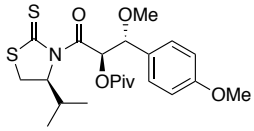
Entry	Substrate	PG	Reaction time (h)	Adduct	Dr[a]	Yield (%)[b]
1	**1**	TES	15	**8a**	90:10	26
2[c]	**2**	TBS	15	**9a**	86:14	49
3	**3**	TBDPS	15	**10a**	75:25	19
4	**4**	Bn	15	**11a**	88:12	61
5	**5**	Me	15	**12a**	89:11	36
6	**6**	Bz	15	**13a**	83:17	73
7	**7**	Piv	15	**14a**	87:13	77
8	**7**	Piv	5	**14a**	87:13	71
9	**7**	Piv	1.5	14a	87:13	57

[a] Established by ^{1}H NMR analysis of the reaction mixtures. [b] Isolated yield of the *anti* adduct after chromatographic purification. [c] TBSOTf was used instead of TESOTf to avoid silyl group exchange.

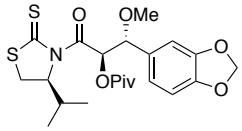
Table 2. Direct addition of **7** to dimethyl acetals of aromatic aldehydes [a]



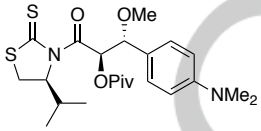
7 **14a–g**



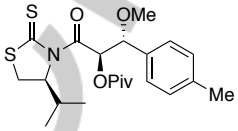
14a
2.5 mol% $(Me_3P)_2NiCl_2$
1.15 equiv TESOTf
dr 87:13 *anti* 77%



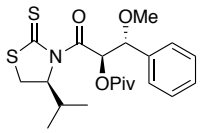
14b
2.5 mol% $(Me_3P)_2NiCl_2$
1.15 equiv TESOTf
dr 81:19 *anti* 79%



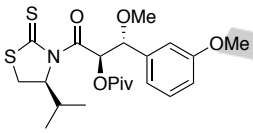
14c
5 mol% $(Me_3P)_2NiCl_2$
2.2 equiv TESOTf
dr 81:19 *anti* 74%



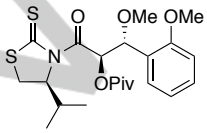
14d
5 mol% $(Me_3P)_2NiCl_2$
2.2 equiv TESOTf
dr 75:25 *anti* 66%



14e
5 mol% $(Me_3P)_2NiCl_2$
2.2 equiv TESOTf
dr 75:25 *anti* 40%



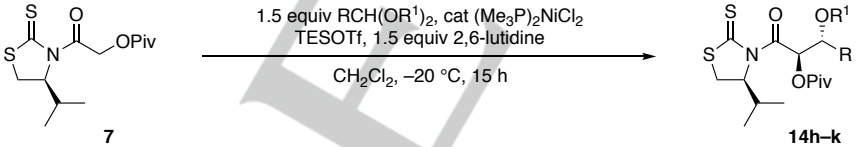
14f
5 mol% $(Me_3P)_2NiCl_2$
2.2 equiv TESOTf
dr 75:25 *anti* 26%



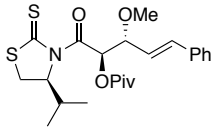
14g
5 mol% $(Me_3P)_2NiCl_2$
2.2 equiv TESOTf
dr 80:20 *anti* 60%

[a] The diastereomeric ratios were established by ^{1}H NMR analysis of the reaction mixtures. The yields indicate the *anti* adduct **14a–g** isolated after chromatographic purification.

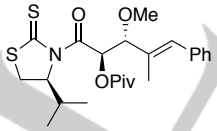
Table 3. Direct addition of **7** to dialkyl acetals of α,β-unsaturated aldehydes [a]



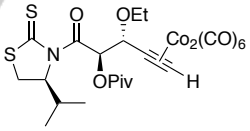
7 **14h–k**



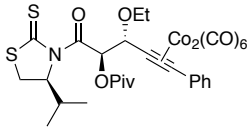
14h
5 mol% $(Me_3P)_2NiCl_2$
1.2 equiv TESOTf
dr 78:22 *anti* 63%



14i
2.5 mol% $(Me_3P)_2NiCl_2$
1.15 equiv TESOTf
dr 93:7 *anti* 89%



14j
5 mol% $(Me_3P)_2NiCl_2$
2.2 equiv TESOTf
dr 85:15 *anti* 79%

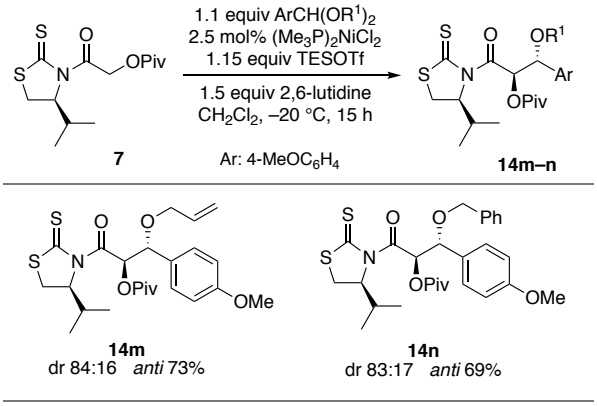


14k
5 mol% $(Me_3P)_2NiCl_2$
2.2 equiv TESOTf
dr 94:6 *anti* 74%

[a] The diastereomeric ratios were established by ^{1}H NMR analysis of the reaction mixtures. The yields indicate the *anti* adduct **14h–k** isolated after chromatographic purification.

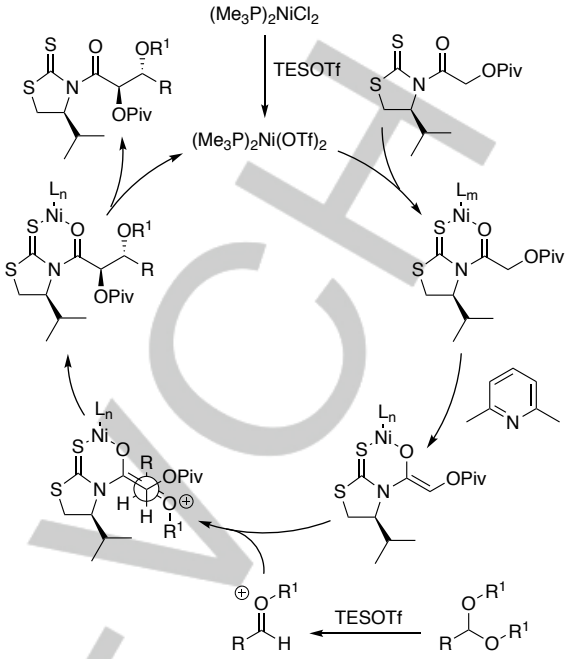
Finally, the search for aldol adducts possessing easily removable protecting groups led us to assess the addition to diallyl and dibenzyl acetals from 4-methoxybenzaldehyde (**m** and **n** respectively). Both acetals performed well and furnished both adducts **14m** and **14n** with high diastereoselectivities and yields, only slightly lower than those obtained with the dimethyl counterpart **a** (Table 4). All together, these examples show that the direct glycolate aldol reaction from chiral thiazolidinethione **7** catalyzed by a nickel(II) complex gives access to *anti* adducts **14** in high yields. These adducts may be considered as protected α,β-dihydroxy carboxylic compounds, which can be easily converted into enantiomerically pure intermediates.[16]

Table 4. Direct addition of **7** to diallyl and dibenzyl acetals of 4-methoxybenzaldehyde [a]



[a] The diastereomeric ratios were established by ^{1}H NMR analysis of the reaction mixtures. The yields indicate the *anti* adduct **14** after chromatographic purification

A mechanistic proposal to account for the stereoselective addition of **7** to acetals is represented in Scheme 2. Taking advantage of Sodeoka's proposal for the conversion of nickel(II) chlorides into the more active triflates by treatment of the former species with R_3SiOTf,[25] we hypothesize that $(Me_3P)_2Ni(OTf)_2$ is the real catalyst of the process. Then, coordination of $(Me_3P)_2Ni(OTf)_2$ to **7** activates the Cα, which can be deprotonated by the base to produce a nickel(II) enolate. At the same time, TESOTf interacts with the acetal and triggers the formation of an oxocarbenium intermediate that finally approaches the less hindered π-face of the enolate in an antiperiplanar manner to produce the *anti* diastereomer.[26]



Scheme 2. Plausible mechanism for the adiition of **7** to dialkyl acetals.

Conclusions

In summary, the direct Lewis acid-mediated reactions of (*S*) 4-isopropyl-*N*-(2-pivaloyloxyacetyl)-1,3-thiazolidine-2-thione with aromatic and α,β-unsaturated dialkyl acetals catalyzed by 2.5–5 mol% of $(Me_3P)_2Ni(OTf)_2$, prepared in situ from commercially available and easy to handle $(Me_3P)_2NiCl_2$, give the corresponding *anti* glycolate diastereomers with a high stereocontrol and yields under mild conditions.

Experimental Section

General Information. Unless otherwise stated, reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen with anhydrous solvents. The solvents and reagents were dried and purified when necessary according to standard procedures. All commercial reagents were used as received. Column chromatography was carried out under low-pressure (flash) conditions and performed on SDS silica gel 60 (35−70 μm). Eluents are indicated in brackets in each case. Analytical thin-layer chromatographies (TLC) were carried out on Merck silica gel 60 F_{254} plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid or 4-methoxybenzaldehyde. R_f values are approximate. Melting points (Mp) were determined with a Stuart Scientific SMP10 or a Gallenkamp apparatus and are uncorrected. Specific rotations ([α]) were determined at 589 nm (D-line) and at 20 °C on a PerkinElmer 241 MC polarimeter. IR spectra were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer. The samples were analyzed as a compacted powder mixed with KBr (solids), over a NaCl tablet (liquid or oil) or using ATR technique (Attenuated Total Reflectance). Only the more representative frequencies (ν) are reported. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Varian Mercury 400 spectrometer or on a Bruker 400. Chemical shifts (δ) are quoted in ppm and referenced to internal TMS (δ

0.00 for ^{1}H NMR) or $CDCl_3$ (δ 77.0 for ^{13}C NMR). Data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad (and their corresponding combinations). When necessary, 2D techniques (COSY and HSQC) were also used to assist with structure elucidation. High-resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer with a TOF analyzer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

Acylation of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione: **Synthesis of (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones 3–5 and 7**

The starting material, (*S*)-4-isopropyl-1,3-thiazolidine-2-thione, was prepared from (*S*)-2-amino-3-methyl-1-butanol according to a procedure reported in the literature.[27]

(*S*)-*N*-(2-*tert*-Butyldiphenylsilyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (3):[16] Neat TBDPSCl (5.2 mL, 20 mmol) was added to a suspension of methyl glycolate (1.56 mL, 16.8 mmol) and imidazole (2.72 g, 40 mmol) in CH_2Cl_2 (20 mL) at 0 °C under N_2 and the reaction mixture was stirred for 36 h at room temperature. It was diluted with Et_2O (100 mL) and washed with H_2O (2 × 30 mL), 2 M HCl (2 × 30 mL), and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated.

A solution of the protected ester in THF (15 mL) was treated with 1 M KOH in 2:1 *v/v* H_2O/MeOH (8.5 mL) and the reaction mixture was stirred for 3 h at 0 °C. It was diluted with Et_2O (70 mL) and washed with H_2O (2 × 50 mL). The aqueous layer was acidified with 2 M HCl until pH 1. Then, it was extracted with Et_2O (2 × 75 mL), the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to give 1.725 g (5.48 mmol, 33% overall yield) of 2-*tert*-butyldiphenylsilyloxyacetic acid, which was used in the next step without further purification.

Oxalyl chloride (0.56 mL, 6.6 mmol) was carefully added to a dry solution of 2-*tert*-butyldiphenylsilyloxyacetic acid (1.23 g, 3.9 mmol) in benzene (6.6 mL) at room temperature under N_2. The resulting solution was stirred for 30 min at room temperature and 30 min at reflux. The organic layer was dried over $MgSO_4$, filtered and concentrated. The volatiles were removed *in vacuo* and the resulting acid chloride was used in the next step without further purification.

A 1.55 M solution of *n*-BuLi in hexanes (2.4 mL, 3.3 mmol) was added dropwise to a solution of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (484 mg, 3.0 mmol) in THF (1.5 mL) at –78 °C under N_2 and the reaction mixture was stirred for 15 min. Then, a solution of 2-*tert*-butyldiphenylsilyloxyacetyl chloride (1.085 g, 3.26 mmol) in THF (1.5 mL) was carefully added and the resulting clear solution was stirred for 5 min at –78 °C and 1.5 h at room temperature. The reaction mixture was cooled with an ice bath and quenched with sat NH_4Cl (1.5 mL). This mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexanes/EtOAc 95:5) to give 783 mg (1.71 mmol, 57% yield) of **3** as a yellow oil. R_f (hexanes/EtOAc 95:5) = 0.20. $[\alpha]_D^{20}$ = +140 (*c* = 0.95, $CHCl_3$). IR (ATR) ν = 2961, 2872, 1716, 1364, 1313, 1114 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.73–7.66 (5H, m), 7.43–7.34 (5H, m), 5.20 (1H, ddd, *J* = 8.1, 6.2, 1.2 Hz), 3.46 (1H, dd, *J* = 11.6, 8.1 Hz), 2.99 (1H, dd, *J* = 11.6, 1.2 Hz), 2.44–2.33 (1H, m), 1.11 (9H, s), 0.98 (3H, d, *J* = 6.9 Hz), 0.90 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.0 (C), 172.1 (C), 135.9 (CH), 135.6 (CH), 133.1 (C), 133.0 (C), 129.8 (CH), 129.7 (CH), 127.7 (CH), 127.6 (CH), 71.4 (CH), 66.8 (CH_2), 31.3 (CH_2), 30.6 (CH), 26.8 (C), 19.3 (CH_3), 19.0 (CH_3), 17.5 (CH_3).

(*S*)-*N*-(2-Benzyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (4):[16] A 1.6 M solution of *n*-BuLi in hexanes (2.4 mL, 3.3 mmol) was added dropwise to a solution of (*S*) 4-isopropyl-1,3-thiazolidine-2-thione (484 mg, 3.0 mmol) in THF (2 mL) at –78 °C under N_2 and the reaction mixture was stirred for 15 min. Then, benzyloxyacetyl chloride (610 μL, 3.9 mmol) was carefully added and the resulting clear solution was stirred for 5 min at –78 °C and 1.5 h at room temperature. The reaction mixture was cooled with an ice bath and quenched with sat NH_4Cl (1.5 mL). This mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with 0.5 M NaOH (3 × 25 mL) and brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (from hexanes/EtOAc 90:10 to 70:30) to give 684 mg (2.33 mmol, 78% yield) of **4** as a yellow oil. R_f (hexanes/EtOAc 70:30) = 0.60. $[\alpha]_D^{20}$ = +234 (*c* = 1.10, $CHCl_3$). IR (ATR) ν = 3059, 3025, 2959, 2872, 1701, 1463, 1363, 1307, 1260 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.42–7.28 (5H, m), 5.18 (1H, ddd, *J* = 8.1, 6.4, 1.0 Hz), 5.05 (1H, d, *J* = 17.7 Hz), 4.97 (1H, d, *J* = 17.7 Hz), 4.67 (1H, d, *J* = 11.6 Hz), 4.63 (1H, d, *J* = 11.6 Hz), 3.59 (1H, dd, *J* = 11.5, 8.1 Hz), 3.08 (1H, dd, *J* = 11.5, 1.0 Hz), 2.45–2.32 (1H, m), 1.07 (3H, d, *J* = 6.8 Hz), 0.99 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.1 (C), 171.0 (C), 137.2 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 73.4 (CH_2), 72.0 (CH_2), 71.3 (CH), 31.4 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.6 (CH_3). HRMS (+ESI): *m/z* calcd for $[M+H]^+$ $C_{15}H_{20}NO_2S_2$: 310.0930, found: 310.0930.

(*S*)-4-Isopropyl-*N*-(2-methoxyacetyl)-1,3-thiazolidine-2-thione (5):[16] An 1.55 M solution of *n*-BuLi in hexanes (2.1 mL, 3.3 mmol) was added dropwise to a solution of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (484 mg, 3.0 mmol) in THF (2 mL) at –78 °C under N_2 and the reaction mixture was stirred for 15 min. Then, methoxyacetyl chloride (360 μL, 3.9 mmol) was carefully added and the resulting clear solution was stirred for 5 min at –78 °C and 1.5 h at room temperature. The reaction mixture was cooled with an ice bath and quenched with sat NH_4Cl (1.2 mL). This mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography (hexanes/EtOAc 95:5) to afford 625 mg (2.68 mmol, 89% yield) of **5** as a yellow oil. R_f (hexanes/EtOAc 95:5) = 0.30. $[\alpha]_D^{20}$ = +313 (*c* = 1.65, $CHCl_3$). IR (ATR) ν = 2963, 1709, 1368, 1313, 1264, 1176, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 5.19 (1H, ddd, *J* = 8.2, 6.2, 1.2 Hz), 4.98 (1H, d, *J* = 17.7 Hz), 4.87 (1H, d, *J* = 17.7 Hz), 3.61 (1H, dd, *J* = 11.6, 8.2 Hz), 3.48 (3H, s), 3.09 (1H, dd, *J* = 11.6, 1.2 Hz), 2.44–2.33 (1H, m), 1.07 (3H, d, *J* = 6.7 Hz), 0.99 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.1 (C), 171.0 (C), 74.5 (CH_2), 71.3 (CH), 59.3 (CH_3), 31.5 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.7 (CH_3).

(*S*)-4-Isopropyl-*N*-(2-pivaloyloxyacetyl)-1,3-thiazolidine-2-thione (7):[16] A mixture of glycolic acid (1.52 g, 20 mmol) and pivaloyl chloride (4.4 mL, 36 mmol) was stirred at room temperature for 60 h under N_2. Then, the volatiles were removed and the resulting *O*-pivaloylglycolic acid was used in the next step without further purification.

A mixture of this acid, (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (2.740 g, 17.0 mmol), EDC·HCl (4.89 g, 25.5 mmol), and DMAP (104 mg, 0.85 mmol) in CH_2Cl_2 (27 mL) was stirred at 0 °C for 15 min and at room temperature for 16 h under N_2. It was diluted in Et_2O (50 mL) and washed with 0.5 M HCl (3 × 40 mL), 0.5 M NaOH (3 × 40 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified through flash chromatography (hexanes/EtOAc 90:10) to afford 4.11 g (13.5 mmol, 80% yield) of **7** as a yellow oil. R_f (hexanes/EtOAc 90:10) = 0.40. $[\alpha]_D$ = +233 (*c* = 1.00, $CHCl_3$). IR (film) ν = 2965, 2874, 1740, 1714, 1141 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.44 (2H, s), 5.11 (1H, ddd, *J* = 8.2, 5.9, 1.2 Hz), 3.63 (1H, dd, *J* = 11.6, 8.2 Hz), 3.09 (1H, dd, *J* = 11.6, 1.2 Hz), 2.43–2.32 (1H, m), 1.27 (9H, s), 1.06 (3H, d, *J* = 6.8 Hz), 0.98 (3H, d, *J* = 7.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 202.5 (C), 177.9 (C), 168.1 (C), 71.4 (CH), 65.0 (CH_2), 38.7 (C), 31.4 (CH), 30.7 (CH_2), 27.1 (CH_3), 19.0 (CH_3), 17.5 (CH_3). HRMS: *m/z* calcd for $[M+H]^+$ $C_{13}H_{22}NO_3S_2$ 304.1036, found 304.1037; *m/z* calcd for $[M+Na]^+$ $C_{13}H_{21}NNaO_3S_2$ 326.0855, found 326.0859.

Deprotection of (*S*)-*N*-(2-benzyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione. Neat $TiCl_4$ (0.5 mL, 4.6 mmol) was added to a solution of **4** (707 mg, 2.3 mmol) in CH_2Cl_2 (18 mL) at room temperature under N_2 and the reaction mixture was stirred for 30 min. The reaction was quenched by addition of sat NH_4Cl (30 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The resulting *N*-acyl thioimide was used in the next step without further purification.

Synthesis of (*S*)-*N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones 1, 2, and 6

(*S*)-4-Isopropyl-*N*-(2-triethylsilyloxyacetyl)-1,3-thiazolidine-2-thione (1):[16] A solution of the deprotected *N*-acyl thioimide, TESOTf (0.65 mL, 2.9 mmol, 1.25 equiv), and 2,6-lutidine (0.35 mL, 3.0 mmol, 1.3 equiv) in CH_2Cl_2 (9.2 mL) was stirred at 0 °C for 5 min and 40 min at room temperature under N_2. The reaction was quenched by addition of neat MeOH (2.5 mL). The resulting mixture was diluted in Et_2O (30 mL). Then, it was washed with sat $NaHCO_3$ (3 × 20 mL), sat $KHSO_4$ (3 × 20 mL), and brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc 90:10) to give 234 mg (0.70 mmol, 30% overall yield) of **1** as a yellow oil. R_f (hexanes/EtOAc 90:10) = 0.35. $[\alpha]_D$ = +180.5 (*c* = 0.67, $CHCl_3$). IR (ATR) ν = 2951, 2870, 1705, 1679, 1464, 1405, 1364, 1264, 1175, 1119 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.18 (1H, ddd, *J* = 8.2, 6.2, 1.2 Hz), 5.16 (1H, d, *J* = 18.2 Hz), 5.10 (1H, d, *J* = 18.2 Hz), 3.59 (1H, dd, *J* = 11.5, 8.2 Hz), 3.08 (1H, dd, *J* = 11.5, 1.2 Hz), 2.45–2.33 (1H, m), 1.06 (3H, d, *J* = 6.8 Hz), 0.98 (3H, d, *J* = 7.1 Hz), 0.98 (9H, t, *J* = 7.8 Hz), 0.66 (6H, q, *J* = 7.8 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 202.0 (C), 172.8 (C), 71.6 (CH), 66.3 (CH_2), 31.4 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.5 (CH_3), 6.7 (CH_3), 4.4 (CH_2).

(*S*)-*N*-(2-*tert*-Butyldimethylsilyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (2):[16] A solution of the deprotected *N*-acyl thioimide, TBSOTf (0.65 mL, 2.9 mmol, 1.25 equiv), and 2,6-lutidine (0.35 mL, 3.0 mmol, 1.3 equiv) in CH_2Cl_2 (9.2 mL) was stirred at 0 °C for 5 min and 40 min at room temperature under N_2. The reaction was quenched by addition of neat MeOH (2.5 mL). The resulting mixture was diluted in Et_2O (30 mL). Then, it was washed with sat $NaHCO_3$ (3 × 20 mL), sat $KHSO_4$ (3 × 20 mL), and brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc 95:5) to give 391 mg (1.17 mmol, 51% overall yield) of **2** as a yellow oil. R_f (hexanes/EtOAc 95:5) = 0.20. $[\alpha]_D$ = +227 (*c* = 0.98, $CHCl_3$). IR (ATR) ν = 2958, 2857, 1715, 1373, 1263, 1178, 1142 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 5.17 (1H, ddd, *J* = 8.2, 6.0, 1.2 Hz), 5.14 (1H, d, *J* = 18.3 Hz), 5.13 (1H, d, *J* = 18.3 Hz), 3.59 (1H, dd, *J* = 11.5, 8.2 Hz), 3.08 (1H, dd, *J* = 11.5, 1.2 Hz), 2.43–2.35 (1H, m), 1.06 (3H, d, *J* = 6.8 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 0.93 (9H, s), 0.12 (3H, s), 0.11 (3H, s). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 202.9 (C), 172.9 (C), 71.6 (CH), 66.7 (CH_2), 31.4 (CH_2), 30.7 (CH), 25.8 (CH_3), 19.0 (CH_3), 18.5 (C), 17.5 (CH_3), –5.3 (CH_3), –5.4 (CH_3).

(*S*)-*N*-(2-Benzoyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (6):[16] A solution of the deprotected *N*-acyl thioimide, benzoyl chloride (1.3 mL, 11.4 mmol, 5 equiv), and 2,6-lutidine (1.3 mL, 11.4 mmol, 5 equiv) in CH_2Cl_2 (9.2 mL) was stirred at 0 °C for 5 min and 40 min at room temperature under N_2.The reaction was quenched by addition of neat MeOH (2.5 mL). The resulting mixture was diluted in Et_2O (30 mL). Then, it was washed with sat $NaHCO_3$ (3 × 20 mL), sat $KHSO_4$ (3 × 20 mL), and brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (from CH_2Cl_2/hexanes 50:50 to 80:20) to give 446 mg (1.38 mmol, 60% overall yield) of **6** as a yellow solid. Mp 93–95 °C. R_f (CH_2Cl_2/hexanes 80:20) = 0.40. $[\alpha]_D$ = +212 (*c* = 1.10, $CHCl_3$). IR (KBr) ν = 2960, 2870, 1726, 1376, 1260, 1183, 1115 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.12–8.09 (2H, m), 7.61–7.43 (3H, m), 5.75 (1H, d, *J* = 16.7 Hz), 5.68 (1H, d, *J* = 16.7 Hz), 5.14 (1H, ddd, *J* = 8.2, 5.9, 1.2 Hz), 3.66 (1H, dd, *J* = 11.6, 8.2 Hz), 3.11 (1H, dd, *J* = 11.6, 1.2 Hz), 2.45–2.34 (1H, m), 1.08 (3H, d, *J* = 6.7 Hz), 0.98 (3H, d, *J* = 6.9 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ = 202.5 (C), 167.9 (C), 166.0 (C), 133.3 (CH), 129.9 (CH), 129.3 (C), 128.4 (CH), 71.5 (CH), 65.6 (CH_2), 31.5 (CH_2), 30.7 (CH), 19.0 (CH_3), 17.5 (CH_3).

General procedure for the direct Ni(II)-catalyzed addition of *N*-glycolyl thiazolidinethiones to acetals

Solid $(Me_3P)_2NiCl_2$ was added to a solution of a *N*-glycolyl thioimide (0.50 mmol) and a dimethyl acetal in CH_2Cl_2 (1.0 mL) under N_2. The resulting mixture was cooled to –20 ºC and TESOTf and 2,6-lutidine (88 μL, 0.75 mmol, 1.5 equivalents) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at –20 ºC for 15 h. It was quenched with sat NH_4Cl (1.2 mL) and then diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude was purified by flash column chromatography to give the desired product.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-3-(4-methoxyphenyl)-2-triethylsilyloxypropanoyl]-1,3-thiazolidine-2-thione (8a): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), (*S*)-4-isopropyl-*N*-(2-triethylsilyloxyacetyl)-1,3-thiazolidine-2-thione (**1**, 167 mg, 0.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (**a**, 94 μL, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (from hexanes/CH_2Cl_2 50:50 to CH_2Cl_2) to give 46 mg (0.13 mmol, 26% yield) of **8a** as a yellow oil. R_f (hexanes/CH_2Cl_2 20:80) = 0.60. $[\alpha]_D^{20}$ = +138 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2951, 2870, 1694, 1605, 1509, 1360, 1238, 1156, 1108 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.39–7.37 (2H, m), 6.89–6.87 (2H, m), 6.70 (1H, *J* = 8.1 Hz), 5.36 (1H, ddd, *J* = 8.0, 6.4, 0.9 Hz), 4.27 (1H, d, *J* = 8.1 Hz), 3.81 (3H, s), 3.50 (1H, dd, *J* = 11.5, 8.0 Hz), 3.10 (3H, s), 3.03 (1H, dd, *J* = 11.5, 0.9 Hz), 2.40–2.31 (1H, m), 1.11 (3H, d, *J* = 6.8 Hz), 1.03 (3H, d, *J* = 6.9 Hz), 0.70 (9H, t, *J* = 7.9 Hz), 0.39–0.22 (6H, m). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 174.8 (C), 159.6 (C), 131.0 (C), 129.7 (CH), 113.4 (CH), 86.8 (CH), 71.8 (CH), 71.3 (CH), 56.6 (CH_3), 55.3 (CH_3), 30.6 (CH), 30.5 (CH_2), 18.9 (CH_3), 17.8 (CH_3), 6.4 (CH_3), 4.4 (CH_2). HRMS (+ESI): *m/z* cald for $[M–OCH_3]^+$ $C_{22}H_{34}NO_3S_2Si$: 452.1744, found: 452.1733; *m/z* calcd for $[M+NH_4]^+C_{23}H_{41}N_2O_4S_2Si$: 501.2272, found: 501.2277; *m/z* calcd for $[M+Na]^+$ $C_{23}H_{37}NNaO_4S_2Si$: 506.1825, found: 506.1834.

(*S*)-*N*-[(2*R*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (9a): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), (*S*)-*N*-(*tert*-butyldimethylsilyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (**2**, 167 mg, 0.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (**a**, 94 μL, 0.55 mmol), and TBSOTf (133 μL, 0.58 mmol). The crude was purified by column chromatography (from hexanes/CH_2Cl_2 50:50 to 40:60) to give 117 mg (0.25 mmol, 49% yield) of **9a** as a yellow oil. R_f (CH_2Cl_2) = 0.65. $[\alpha]_D^{20}$ = +141 (*c* = 0.96, $CHCl_3$). IR (film) ν = 2930, 2858, 1704, 1512, 1364, 1250, 1163, 1121 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.39–7.37 (2H, m), 6.89–6.87 (2H, m), 6.75 (1H, d, *J* = 8.1 Hz), 5.39 (1H, ddd, *J* = 8.1, 6.2, 1.2 Hz), 4.26 (1H, d, *J* = 8.1 Hz), 3.81 (3H, s), 3.50 (1H, dd, *J* = 11.5, 8.1 Hz), 3.10 (3H, s), 3.03 (1H, dd, *J* = 11.5, 1.2 Hz), 2.42–2.30 (1H, m), 1.11 (3H, d, *J* = 6.8 Hz), 1.03 (3H, d, *J* = 6.9 Hz), 0.72 (9H, s), –0.22 (3H, s), –0.39 (3H, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 174.8 (C), 159.6 (C), 131.0 (C), 129.8 (CH), 113.4 (CH), 86.9 (CH), 71.8 (CH), 71.7 (CH), 56.6 (CH_3), 55.3 (CH_3), 30.6 (CH), 30.4 (CH_2), 25.5 (CH_3), 18.9 (CH_3), 17.9 (C), 17.7 (CH_3), –5.2 (CH_3), –5.4 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OMe]^+$

$C_{22}H_{34}NO_3S_2Si$: 452.1744, found: 452.1741, calcd for $[M+Na]^+$ $C_{23}H_{37}NNaO_4S_2Si$: 506.1825, found:506.1825.

(*S*)-*N*-[(2*R*,3*R*)-2-(*tert*-Butyldiphenylsilyloxy)-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (10a): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), (*S*)-*N*-(*tert*-butyldiphenylsilyloxyacetyl)-4-isopropyl-1,3-thiazolidine-2-thione (**3**, 229 mg, 0.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (**a**, 94 μL, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (hexanes/CH_2Cl_2 60:40) to give 58 mg (0.10 mmol, 19% yield) of **10a** as a yellow oil. R_f (hexanes/CH_2Cl_2 60:40) = 0.45. $[\alpha]_D^{20}$ = +119 (*c* = 0.90, $CHCl_3$). IR (ATR) ν = 2955, 2925, 2851, 1694, 1609, 1505, 1360, 1234, 1164, 1112 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.62–7.60 (2H, m), 7.48–7.45 (2H, m), 7.42–7.29 (4H, m), 7.16–7.12 (2H, m), 7.00–6.98 (2H, m), 6.95–6.93 (2H, m), 6.80 (1H, d, *J* = 7.6 Hz), 4.71 (1H, ddd, *J* = 8.3, 5.7, 1.2 Hz), 4.36 (1H, d, *J* = 7.6 Hz), 3.87 (3H, s), 3.09 (3H, s), 2.78 (1H, dd, *J* = 11.2, 8.3 Hz), 2.67 (1H, dd, *J* = 11.2, 1.2 Hz), 2.20–2.12 (1H, m), 0.95 (3H, d, *J* = 6.8 Hz), 0.93 (9H, s), 0.90 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 201.6 (C), 174.06 (C), 159.8 (C), 136.1 (CH), 135.7 (CH), 133.3 (C), 132.5 (C), 131.1 (C), 130.1 (CH), 129.7 (CH), 129.4 (CH), 127.3 (CH), 127.2 (CH), 113.6 (CH), 87.4 (CH), 72.0 (CH), 71.2 (CH), 56.5 (CH_3), 55.3 (CH_3), 30.4 (CH), 29.2 (CH_2), 26.8 (CH_3), 19.0 (C), 18.8 (CH_3), 17.1 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OCH_3]^+$ $C_{32}H_{38}NO_3S_2Si$: 576.2057, found: 576.2052; *m/z* calcd for $[M+Na]^+$ $C_{33}H_{41}NNaO_4S_2Si$: 630.2138, found: 630.2141.

(*S*)-*N*-[(2*R*,3*R*)-2-Benzyloxy-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (11a): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), (*S*)-*N*-benzyloxyacetyl-4-isopropyl-1,3-thiazolidine-2-thione (**4**, 155 mg, 0.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (**a**, 94 μL, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (from hexanes/CH_2Cl_2 30:70 to CH_2Cl_2) to give 142 mg (0.31 mmol, 61% yield) of **11a** as a yellow oil. R_f (CH_2Cl_2) = 0.50. $[\alpha]_D^{20}$ = +151 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2959, 2925, 2866, 1694, 1606, 1509, 1245, 1168, 1093, 1027 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.44–7.41 (2H, m), 7.26–7.24 (3H, m), 7.14–7.12 (2H, m), 6.92–6.90 (2H, m), 6.54 (1H, d, *J* = 8.2 Hz), 5.03 (1H, ddd, *J* = 8.1, 6.1, 1.1 Hz), 4.40 (1H, d, *J* = 12.1 Hz), 4.37 (1H, d, *J* = 8.2 Hz), 4.17 (1H, d, *J* = 12.1 Hz), 3.84 (3H, s), 3.18 (1H, dd, *J* = 11.3, 8.1 Hz), 3.10 (3H, s), 2.88 (1H, dd, *J* = 11.3, 1.1 Hz), 2.30–2.22 (1H, m), 1.03 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 173.5 (C), 159.6 (C), 137.4 (C), 130.7 (C), 129.6 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 113.6 (CH), 85.0 (CH), 78.1 (CH), 73.7 (CH_2), 71.5 (CH), 56.6 (CH_3), 55.2 (CH_3), 30.5 (CH), 30.3 (CH_2), 18.8 (CH_3), 17.5 (CH_3); HRMS (+ESI): *m/z* calcd for $[M–OCH_3]^+$ $C_{23}H_{26}NO_3S_2$: 428.1349, found: 428.1346; *m/z* calcd for $[M+Na]^+$ $C_{24}H_{29}NNaO_4S_2$: 482.1430, found: 482.1425.

(*S*)-*N*-[(2*R*,3*R*)-2,3-Dimethoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (12a): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), (*S*)-4-isopropyl-*N*-methoxyacetyl-1,3-thiazolidine-2-thione (**5**, 117 mg, 0.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (**a**, 94 μL, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (from hexanes/CH_2Cl_2 40:60 to CH_2Cl_2) to give 70 mg (0.18 mmol, 36% yield) of **12a** as a yellow oil. R_f (CH_2Cl_2) = 0.40. $[\alpha]_D^{20}$ = +161 (*c* = 1.04, $CHCl_3$). IR (ATR) ν = 2959, 2929, 2821, 1690, 1608, 1509, 1360, 1238, 1160, 1093 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.39–7.37 (2H, m), 6.91–6.89 (2H, m), 6.48 (1H, d, *J* = 7.7 Hz), 5.39 (1H, ddd, *J* = 8.5, 5.5, 1.2 Hz), 4.37 (1H, d, *J* = 7.7 Hz), 3.81 (3H, s), 3.53 (1H, dd, *J* = 11.5, 8.5 Hz), 3.15 (3H, s), 3.11 (3H, s), 3.04 (1H, dd, *J* = 11.5, 1.2 Hz), 2.38–2.26 (1H, m), 1.11 (3H, d, *J* = 6.8 Hz), 1.10 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.9 (C), 173.3 (C), 159.6 (C), 130.3 (C), 129.6 (CH), 113.6 (CH), 84.7 (CH), 80.4 (CH), 71.8 (CH), 58.8 (CH_3), 56.4 (CH_3), 55.2 (CH_3), 30.6 (CH), 29.8 (CH_2), 19.0 (CH_3), 17.2 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OCH_3]^+$ $C_{17}H_{22}NO_3S_2$: 352.1036, found: 352.1031; *m/z* calcd for $[M+Na]^+$ $C_{18}H_{25}NNaO_4S_2$: 406.1117, found: 406.1105.

(*S*)-*N*-[(2*R*,3*R*)-2-Benzoyloxy-3-methoxy-3-(4-methoxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (13a): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), (*S*)-*N*-benzoyloxyacetyl-4-isopropyl-1,3-thiazolidine-2-thione (**6**, 162 mg, 0.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (94 μL, 0.55 mmol) and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (hexanes/CH_2Cl_2 40:60) to give 173 mg (0.37 mmol, 73% yield) of **13a** as a yellow oil. R_f (hexanes/CH_2Cl_2 20:80) = 0.60. $[\alpha]_D^{20}$ = +129 (*c* = 0.93, $CHCl_3$). IR (ATR) ν = 2962, 2925, 2825, 1716, 1694, 1605, 1512, 1449, 1360, 1245, 1171, 1108, 1090, 1026 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.93–7.90 (2H, m), 7.55–7.46 (3H, m), 7.43 (1H, d, *J* = 7.4 Hz), 7.41–7.37 (2H, m), 6.94–6.92 (2H, m), 5.32 (1H, ddd, *J* = 8.1, 6.0, 1.0 Hz), 4.75 (1H, d, *J* = 7.4 Hz), 3.81 (3H, s), 3.65 (1H, dd, *J* = 11.5, 8.1 Hz), 3.21 (3H, s), 3.04 (1H, dd, *J* = 11.5, 1.0 Hz), 2.41–2.29 (1H, m), 1.13 (3H, d, *J* = 6.8 Hz), 1.03 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.8 (C), 170.2 (C), 165.8 (C), 159.8 (C), 133.3 (CH), 129.8 (CH), 129.5 (C), 129.5 (CH), 129.0 (C), 128.3 (CH), 113.7 (CH), 83.5 (CH), 73.6 (CH), 71.7 (CH), 56.8 (CH_3), 55.2 (CH_3), 30.5 (CH), 30.5 (CH_2), 18.9 (CH_3), 17.6 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OCH_3]^+$ $C_{23}H_{24}NO_4S_2$: 442.1141, found: 442.1134; *m/z* calcd for $[M+Na]^+$ $C_{24}H_{27}NNaO_5S_2$: 496.1223, found: 496.1224.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-3-(4-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (14a): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), (*S*)-4-isopropyl-*N*-pivaloyloxyacetyl-1,3-thiazolidine-2-thione (**7**, 152 mg, 0.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (**a**, 94 μL, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (hexanes/EtOAc 85:15) to give 175 mg (0.39 mmol, 77% yield) of **14a** as a yellow solid. Mp 129–130 ºC. R_f (hexanes/EtOAc 85:15) = 0.40. $[\alpha]_D^{20}$ = +172 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2966, 2929, 2862, 2825, 1727, 1701, 1606, 1512, 1360, 1245, 1171, 1145 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.39–7.37 (2H, m), 7.13 (1H, d, *J* = 7.4 Hz), 6.90–6.88 (2H, m), 5.29 (1H, ddd, *J* = 8.3, 5.9, 1.0 Hz), 4.60 (1H, d, *J* = 7.4 Hz), 3.81 (3H, s), 3.60 (1H, dd, *J* = 11.4, 8.3 Hz), 3.17 (3H, s), 3.01 (1H, dd, *J* = 11.4, 1.0 Hz), 2.36–2.27 (1H, m), 1.11 (3H, d, *J* = 6.8 Hz), 1.10 (9H, s), 1.01 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 177.5 (C), 170.3 (C), 159.7 (C), 129.4 (CH), 129.4 (C), 113.5 (CH), 83.4 (CH), 73.1 (CH), 71.6 (CH), 56.7 (CH_3), 55.2 (CH_3), 38.3 (C), 30.5 (CH), 30.2 (CH_2), 26.8 (CH_3), 18.9 (CH_3), 17.4 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OCH_3]^+$ $C_{21}H_{28}NO_4S_2$: 422.1454, found: 422.1445; *m/z* calcd for $[M+Na]^+$ $C_{22}H_{31}NNaO_5S_2$: 476.1536, found: 476.1531.

(*S*)-*N*-[(2*R*,3*R*)-3-(Benzo[*d*][1,3]dioxol-5-yl)-3-methoxy-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (14b): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), **7** (152 mg, 0.5 mmol), piperonal dimethyl acetal (**b**, 108 mg, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (from hexanes/EtOAc 88:12 to 84:16) to give 186 mg (0.40 mmol, 79% yield) of **14b** as a yellow solid. Mp 132–133 ºC. R_f (hexanes/EtOAc 80:20) = 0.45. $[\alpha]_D^{20}$ = +187 (*c* = 1.25, $CHCl_3$). IR (ATR) ν = 2959, 2925, 2870, 1724, 1705, 1480, 1438, 1337, 1249, 1156, 1030 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.11 (1H, d, *J* = 7.4 Hz), 7.03 (1H, d, *J* = 1.6 Hz), 6.86 (1H, dd, *J* = 7.9, 1.6 Hz), 6.77 (1H, d, *J* = 7.9 Hz), 5.98–5.95 (2H, m), 5.29 (1H, ddd,

J = 8.3, 5.9, 1.0 Hz), 4.57 (1H, d, *J* = 7.4 Hz), 3.60 (1H, dd, *J* = 11.5, 8.3 Hz), 3.18 (3H, s), 3.02 (1H, dd, *J* = 11.5, 1.0 Hz), 2.37–2.25 (1H, m), 1.12 (9H, s), 1.09 (3H, d, *J* = 6.9 Hz), 1.01 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 177.5 (C), 170.1 (C), 147.7 (2 × C), 131.3 (C), 122.1 (CH), 108.1 (CH), 107.6 (CH), 101.0 (CH_2), 83.6 (CH), 72.9 (CH), 71.6 (CH), 56.7 (CH_3), 38.3 (C), 30.5 (CH), 30.2 (CH_2), 26.8 (CH_3), 18.8 (CH_3), 17.4 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OCH_3]^+$ $C_{21}H_{26}NO_5S_2$: 436.1247, found: 436.1247.

(*S*)-*N*-[(2*R*,3*R*)-3-(4-Dimethylaminophenyl)-3-methoxy-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (14c): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol%), **7** (152 mg, 0.5 mmol), 4-dimethylaminobenzaldehyde dimethyl acetal (**c**, 107 mg, 0.55 mmol), and TESOTf (249 μL, 1.10 mmol). The crude was purified by column chromatography (from hexanes/EtOAc 90:10 to 80:20) to give 172 mg (0.37 mmol, 74% yield) of **14c** as a yellow solid. Mp 136–137 ºC. R_f (hexanes/EtOAc 80:20) = 0.45. $[\alpha]_D^{20}$ = +165 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2973, 2954, 2870, 1720, 1702, 1613, 1523, 1360, 1182, 1149 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.32–7.30 (2H, m), 7.13 (1H, d, *J* = 7.4 Hz), 6.71–6.69 (2H, m), 5.30 (1H, ddd, *J* = 8.4, 5.7, 1.0 Hz), 4.54 (1H, d, *J* = 7.4 Hz), 3.59 (1H, dd, *J* = 11.4, 8.4 Hz), 3.16 (3H, s), 3.00 (1H, dd, *J* = 11.4, 1.0 Hz), 2.96 (6H, s), 2.37–2.26 (1H, m), 1.11 (3H, d, *J* = 6.6 Hz), 1.11 (9H, s), 1.01 (3H, d, *J* = 6.9 Hz), ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.4 (C), 177.6 (C), 170.5 (C), 150.5 (C), 129.1 (CH), 124.8 (C), 111.8 (CH), 83.7 (CH), 73.3 (CH), 71.6 (CH), 56.5 (CH_3), 40.4 (CH_3), 38.3 (C), 30.5 (CH), 30.1 (CH_2), 26.8 (CH_3), 18.9 (CH_3), 17.4 (CH_3) HRMS (+ESI): *m/z* calcd for $[M–OCH_3]^+$ $C_{22}H_{31}N_2O_3S_2$: 435.1771, found: 435.1784; *m/z* calcd for $[M+H]^+$ $C_{23}H_{35}N_2O_4S_2$: 467.2033, found: 467.2047.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-2-pivaloyloxy-3-(4-tolyl)propanoyl]-1,3-thiazolidine-2-thione (14d): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol%), **7** (152 mg, 0.5 mmol), 4-methylbenzaldehyde dimethyl acetal (**d**, 91 mg, 0.55 mmol), and TESOTf (249 μL, 1.10 mmol). The crude was purified by column chromatography (from hexanes/CH_2Cl_2 50:50 to 10:90) to give 145 mg (0.33 mmol, 66% yield) of **14d** as a yellow solid. Mp 139–140 ºC. R_f (hexanes/CH_2Cl_2 10:90) = 0.60. $[\alpha]_D^{20}$ = +196 (*c* = 0.75, $CHCl_3$). IR (ATR) ν = 2959, 2928, 1724, 1694, 1464, 1357, 1305, 1257, 1171, 1145 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.35–7.33 (2H, m), 7.17–7.15 (2H, m), 7.12 (1H, d, *J* = 7.3 Hz), 5.29 (1H, ddd, *J* = 8.4, 5.6, 1.1 Hz), 4.62 (1H, d, *J* = 7.3 Hz), 3.59 (1H, dd, *J* = 11.4, 8.4 Hz), 3.18 (3H, s), 3.01 (1H, dd, *J* = 11.4, 1.1 Hz), 2.37–2.28 (1H, m), 2.35 (3H, s), 1.11 (3H, d, *J* = 7.0 Hz), 1.10 (9H, s), 1.02 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.5 (C), 177.5 (C), 170.2 (C), 138.2 (C), 134.3 (C), 128.8 (CH), 128.1 (CH), 83.6 (CH), 73.1 (CH), 71.6 (CH), 56.8 (CH_3), 38.3 (C), 30.5 (CH), 30.2 (CH_2), 26.8 (CH_3), 21.2 (CH_3), 18.9 (CH_3), 17.4 (CH_3); HRMS (+ESI): *m/z* calcd for $[M+H]^+$ $C_{22}H_{32}NO_4S_2$: 438.1767, found: 438.1772; *m/z* calcd for $[M+Na]^+$ $C_{22}H_{31}NNaO_4S_2$: 460.1587, found: 460.1595.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-3-phenylpropanoyl-2-pivaloyloxy]-1,3-thiazolidine-2-thione (14e):[16] The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol%), **7** (152 mg, 0.5 mmol), benzaldehyde dimethyl acetal (**e**, 83 μL, 0.55 mmol), and TESOTf (249 μL, 1.10 mmol). The crude was purified by column chromatography twice (first, from hexanes/EtOAc 93:7 to 85:15; finally, from hexanes/CH_2Cl_2 70:30 to 15:85) to give 84 mg (0.20 mmol, 40% yield) of **14e** as a yellow solid. Mp 142–143 ºC. R_f (hexanes/EtOAc 85:15) = 0.45. $[\alpha]_D^{20}$ = +211 (*c* = 1.15, $CHCl_3$). IR (KBr) ν = 2962, 1728, 1707, 1368, 1178, 1149 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.47–7.44 (2H, m), 7.38–7.30 (3H, m), 7.15 (1H, d, *J* = 7.6 Hz), 5.30 (1H, ddd, *J* = 8.3, 5.9, 1.0 Hz), 4.64 (1H, d, *J* = 7.6 Hz), 3.60 (1H, dd, *J* = 11.4, 8.3 Hz), 3.20 (3H, s), 3.02 (1H, dd, *J* = 11.4, 1.0 Hz), 2.39–2.27 (1H, m), 1.12 (3H, d, *J* = 6.8 Hz), 1.08 (9H, s), 1.02 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 177.5 (C), 170.3 (C), 137.5 (C), 128.5 (CH), 128.2 (CH), 128.1 (CH), 83.9 (CH), 73.0 (CH), 71.7 (CH), 56.9 (CH3), 38.3 (C), 30.6 (CH), 30.3 (CH_2), 26.8 (CH_3), 18.9 (CH_3), 17.5 (CH_3). HRMS (+ESI): *m/z* calcd for $[M+H]^+$ $C_{21}H_{30}NO_4S_2$: 424.1611, found: 424.1625.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-3-(3-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (14f):[16] The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol%), **7** (152 mg, 0.5 mmol), 3-methoxybenzaldehyde dimethyl acetal (**f**, 100 mg, 0.55 mmol), and TESOTf (249 μL, 1.10 mmol). The crude was purified by column chromatography (hexanes/EtOAc 85:15) to give 59 mg (0.13 mmol, 26% yield) of **14f** as a yellow solid. Mp 85–88 ºC. R_f (hexanes/EtOAc 85:15) = 0.35. $[\alpha]_D^{20}$ = +247 (*c* = 0.90, $CHCl_3$). IR (KBr) ν = 3005, 2968, 2868, 1735, 1698, 1486, 1145, 1095 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.28–7.22 (1H, m), 7.14 (1H, d, *J* = 7.6 Hz), 7.14 (1H, dd, *J* = 2.6, 1.5 Hz), 7.02 (1H, dt, *J* = 7.6, 1.5 Hz), 6.86 (1H, ddd, *J* = 8.3, 2.6, 1.5 Hz), 5.30 (1H, ddd, *J* = 8.3, 5.9, 1.1 Hz), 4.61 (1H, d, *J* = 7.6 Hz), 3.82 (3H, s), 3.60 (1H, dd, *J* = 11.4, 8.3 Hz), 3.20 (3H, s), 3.02 (1H, dd, *J* = 11.4, 1.1 Hz), 2.39–2.27 (1H, m), 1.12 (3H, d, *J* = 6.8 Hz), 1.10 (9H, s), 1.02 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 177.5 (C), 170.3 (C), 159.6 (C), 139.2 (C), 129.0 (CH), 120.7 (CH), 114.5 (CH), 113.0 (CH), 83.9 (CH), 72.9 (CH), 71.7 (CH), 56.9 (CH_3), 55.2 (CH_3), 38.3 (C), 30.5 (CH), 30.3 (CH_2), 26.8 (CH_3), 19.0 (CH_3), 17.5 (CH_3). HRMS (+ESI): *m/z* calcd for $[M+H]^+$ $C_{22}H_{32}NO_5S_2$: 422.1454, found: 422.1453; *m/z* calcd for $[M+Na]^+$ $C_{22}H_{31}NNaO_5S_2$: 476.1536, found: 476.1539.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-3-(2-methoxyphenyl)-2-pivaloyloxypropanoyl]-1,3-thiazolidine-2-thione (14g): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol%), **7** (152 mg, 0.5 mmol), 2-methoxybenzaldehyde dimethyl acetal (**g**, 100 mg, 0.55 mmol), and TESOTf (249 μL, 1.10 mmol). The crude was purified by column chromatography (from hexanes/CH_2Cl_2 50:50 to 20:80) to give 120 mg (0.30 mmol, 60% yield) of **14g** as a yellow solid. Mp 125–126 ºC. R_f (hexanes/CH_2Cl_2 20:80) = 0.45. $[\alpha]_D^{20}$ = +143 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2955, 2929, 2870, 1724, 1698, 1598, 1586, 1486, 1457, 1360, 1264, 1242, 1160 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.62 (1H, dd, *J* = 7.5, 1.8 Hz), 7.29 (1H, ddd, *J* = 8.3, 7.5, 1.8 Hz), 7.01 (1H, td, *J* = 7.5, 1.1 Hz), 6.96 (1H, d, *J* = 5.8 Hz), 6.85 (1H, dd, *J* = 8.3, 1.1 Hz), 5.43 (1H, d, *J* = 5.8 Hz), 5.16 (1H, ddd, *J* = 8.4, 5.3, 1.0 Hz), 3.78 (3H, s), 3.61 (1H, dd, *J* = 11.4, 8.4 Hz), 3.22 (3H, s), 3.01 (1H, dd, *J* = 11.4, 1.0 Hz), 2.39–2.28 (1H, m), 1.11 (3H, d, *J* = 6.8 Hz), 1.08 (9H, s), 1.00 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 177.9 (C), 169.6 (C), 157.8 (C), 129.5 (CH), 129.3 (CH), 125.0 (C), 120.5 (CH), 110.0 (CH), 75.5 (CH), 73.4 (CH), 72.0 (CH), 56.9 (CH_3), 55.3 (CH_3), 38.5 (C), 30.8 (CH), 30.1 (CH_2), 26.8 (CH_3), 19.0 (CH_3), 17.2 (CH_3). HRMS (+ESI): *m/z* calcd for $[M+Na]^+$ $C_{22}H_{31}NNaO_5S_2$: 476.1536, found: 476.1536.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-5-phenyl-2-pivaloyloxy-4-pentenoyl]-1,3-thiazolidine-2-thione (14h). The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol%), **7** (152 mg, 0.5 mmol), (*E*)-cinnamaldehyde dimethyl acetal (**h**, 98 mg, 0.55 mmol), and TESOTf (136 μL, 0.60 mmol). The crude was purified by column chromatography (hexanes/CH_2Cl_2 30:70) to give 142 mg (0.31 mmol, 63% yield) of **14h** as a yellow oil. R_f (CH_2Cl_2) = 0.45. $[\alpha]_D^{20}$ = +197 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2962, 2925, 2866, 1731, 1698, 1475, 1460, 1360, 1260, 1175, 1145 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.25 (5H, m), 6.96 (1H, d, *J* = 4.8 Hz), 6.60 (1H, d, *J* = 16.0 Hz), 6.25 (1H, dd, *J* = 16.0, 8.4 Hz), 5.23 (1H, ddd, *J* = 8.4, 6.0, 1.1 Hz), 4.41 (1H, dd, *J* = 8.4, 4.8 Hz), 3.61 (1H, dd, *J* = 11.5, 8.4, Hz), 3.35 (3H, s), 3.01 (1H, dd, *J* = 11.5, 1.1 Hz), 2.31–2.19 (1H, m), 1.23 (9H, s),1.06 (3H, d, *J* = 6.8 Hz), 0.94 (3H,d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.4 (C), 177.8 (C), 168.8 (C), 136.1 (C), 135.3 (CH), 128.6 (CH), 128.1 (CH), 126.7 (CH), 124.6 (CH), 81.6 (CH), 73.5 (CH), 71.6 (CH), 56.8 (CH_3), 38.7 (C),

30.5 (CH), 30.5 (CH_2), 27.0 (CH_3), 18.9 (CH_3), 17.5 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OCH_3]^+$ $C_{22}H_{28}NO_3S_2$: 418.1505, found: 418.1518.

(*S*)-4-Isopropyl-*N*-[(2*R*,3*R*)-3-methoxy-4-methyl-5-phenyl-2-pivaloyloxy-4-pentenoyl]-1,3-thiazolidine-2-thione (14i): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), **7** (152 mg, 0.5 mmol), (*E*)-α-methylcinnamaldehyde dimethyl acetal (**i**, 106 mg, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (hexanes/EtOAc 92:8) to give 203 mg (0.45 mmol, 89% yield) of **14i** as a yellow oil. R_f (hexanes/EtOAc 85:15) = 0.45. $[\alpha]_D^{20}$ = +222 (*c* = 2.10, $CHCl_3$). IR (film) ν = 2966, 2874, 1732, 1700, 1364, 1176, 1149cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.37–7.19 (5H, m), 7.20 (1H, d, *J* = 7.5 Hz), 6.54 (1H, br s), 5.31 (1H, ddd, *J* = 8.5, 5.7, 1.1 Hz), 4.26 (1H, d, *J* = 7.5 Hz), 3.57 (1H, dd, *J* = 11.5, 8.5 Hz), 3.25 (3H, s), 2.99 (1H, dd, *J* = 11.5, 1.1 Hz), 2.32–2.22 (1H, m), 1.66 (3H, d, *J* = 1.3 Hz), 1.19 (9H, s), 1.05 (3H, d, *J* = 6.8 Hz), 0.96 (3H,d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.5 (C), 177.6 (C), 170.3 (C), 136.8 (C), 134.5 (C), 131.4 (CH), 128.9 (CH), 128.1 (CH), 126.8 (CH), 87.5 (CH), 71.6 (CH), 70.8 (CH), 56.3 (CH_3), 38.4 (C), 30.5 (CH), 29.9 (CH_2), 26.9 (CH_3), 18.8 (CH_3), 17.1 (CH_3), 13.2 (CH_3). HRMS (+ESI): *m/z* calcd for $[M+Na]^+$ $C_{24}H_{33}NNaO_4S_2$:486.1744, found: 486.1742.

(*S*)-*N*-[(2*R*,3*R*)-Hexacarbonyl[μ-η^4-(3-ethoxy-2-pivaloyloxy-4-pentynoyl)dicobalt(Co-Co)]-4-isopropyl-1,3-thiazolidine-2-thione (14j): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol%), **7** (152 mg, 0.5 mmol), hexacarbonyl μ-[η^4-(1,1-diethoxypropyne)]dicobalt (**j**, 311 mg, 0.75 mmol), and TESOTf (249 μL, 1.10 mmol). The crude was purified by column chromatography (hexanes/EtOAc 90:10) to give 264 mg (0.39 mmol, 79% yield) of **14j** as a deep maroon solid. Mp 115–116 ºC. R_f (hexanes/EtOAc 90:10) = 0.35. IR (ATR) ν = 2962, 2870, 2091, 2046, 2017, 1998, 1720, 1683, 1357, 1283, 1179, 1134, 1090 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 6.84 (1H, d, *J* = 7.8 Hz), 6.02 (1H, d, *J* = 0.8 Hz), 5.20 (1H, ddd, *J* = 8.1, 5.9, 0.9 Hz), 4.98 (1H, dd, *J* = 7.8, 0.8 Hz), 3.81 (1H, dq, *J* = 8.6, 7.0 Hz), 3.63 (1H, dd, *J* = 11.4, 8.1 Hz), 3.60 (1H, dq, *J* = 8.6, 7.0 Hz), 3.03 (1H, dd, *J* = 11.4, 0.9 Hz), 2.42–2.34 (1H, m), 1.24 (9H, s), 1.17 (3H, t, *J* = 7.0 Hz), 1.10 (3H, d, *J* = 6.8 Hz), 1.04 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.8 (C), 199.4 (C), 177.7 (C), 169.7 (C), 91.0 (C), 79.5 (CH), 73.3 (CH), 72.5 (CH), 71.7 (CH), 66.6 (CH_2), 38.5 (C), 30.8 (CH), 30.5 (CH_2), 27.0 (CH_3), 19.1 (CH_3), 17.5 (CH_3), 14.7 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OC_2H_5]^+$ $C_{22}H_{22}Co_2NO_9S_2$: 625.9394, found: 625.9394; *m/z* calcd for $[M+Na]^+$ $C_{24}H_{27}Co_2NNaO_{10}S_2$: 693.9633, found: 693.9640.

(*S*)-*N*-[(2*R*,3*R*)-Hexacarbonyl[μ-η^4-(3-ethoxy-5-phenyl-2-pivaloyloxy-4-pentynoyl)dicobalt(Co-Co)]-4-isopropyl-1,3-thiazolidine-2-thione (14k): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (7.0 mg, 25 μmol, 5 mol%), **7** (152 mg, 0.5 mmol), hexacarbonyl μ-[η^4-(1,1-diethoxy-3-phenylpropyne)]dicobalt (**k**, 368 mg, 0.75 mmol), and TESOTf (249 μL, 1.10 mmol). The crude was purified by column chromatography (from hexanes/CH_2Cl_2 50:50 to 30:70) to give 277 mg (0.37 mmol, 74% yield) of **14k** as a deep maroon solid. Mp 109–111 ºC. R_f (hexanes/CH_2Cl_2 30:70) = 0.50. IR (ATR) ν = 2960, 2922, 2090, 2045, 2011, 1727, 1706, 1362, 1169, 1122 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.76–7.74 (2H, m), 7.35–7.26 (3H, m), 6.56 (1H, d, *J* = 1.9 Hz), 5.88 (1H, d, *J* = 1.9 Hz), 5.20 (1H, ddd, *J* = 8.5, 5.4, 1.2 Hz), 3.80 (1H, dq, *J* = 8.7, 7.0 Hz), 3.66 (1H, dd, *J* = 11.5, 8.5 Hz), 3.56 (1H, dq, *J* = 8.7, 7.0 Hz), 3.07 (1H, dd, *J* = 11.5, 1.2 Hz), 2.44–2.32 (1H, m), 1.21 (3H, t, *J* = 7.0 Hz), 1.11 (3H, d, *J* = 6.9 Hz), 1.04 (9H, s), 1.01 (3H, d, *J* = 6.9 Hz), 0.89 (9H, s). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 203.1 (C), 199.3 (C), 178.9 (C), 167.7 (C), 137.7 (C), 130.4 (CH), 128.6 (CH), 127.7 (CH), 93.6 (C), 91.1 (C), 79.5 (CH), 75.5 (CH), 72.5 (CH), 68.2 (CH_2), 38.5 (C), 30.7(CH), 30.5 (CH_2), 26.5 (CH_3), 19.1 (CH_3), 17.1 (CH_3), 15.0 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OC_2H_5–CO]^+$ $C_{22}H_{26}Co_2NO_3S_2$: 534.0013, found: 534.0000; *m/z* calcd for $[M–OC_2H_5]^+$ $C_{28}H_{26}Co_2NO_9S_2$: 701.9707, found: 701.9704.

(*S*)-*N*-[(2*R*,3*R*)-3-Allyloxy-3-(4-methoxyphenyl)-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (14m): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), **7** (152 mg, 0.5 mmol), 4-methoxybenzaldehyde diallyl acetal (**m**, 129 mg, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (from hexanes/CH_2Cl_2 80:20 to 40:60) to give 179 mg (0.36 mmol, 73% yield) of **14m** as a yellow solid. Mp 89–90 ºC. R_f (hexanes/CH_2Cl_2 40:60) = 0.35. $[\alpha]_D^{20}$ = +241 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2962, 2929, 2873, 1720, 1702, 1609, 1509, 1357, 1257, 1175, 1149 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40–7.38 (2H, m), 7.07 (1H, d, *J* = 7.4 Hz), 6.89–6.87 (2H, m), 5.82–5.72 (1H, m), 5.25 (1H, ddd, *J* = 8.2, 6.0, 0.9 Hz), 5.21 (1H, dq, *J* = 17.2, 1.6 Hz), 5.10 (1H, dq, *J* = 10.5, 1.6 Hz), 4.80 (1H, d, *J* = 7.4 Hz), 3.91 (1H, ddt, *J* = 12.9, 4.7, 1.6 Hz), 3.81 (3H, s), 3.75 (1H, ddt, *J* = 12.9, 6.1, 1.6 Hz), 3.61 (1H, dd, *J* = 11.4, 8.2 Hz), 3.01 (1H, dd, *J* = 11.4, 0.9 Hz), 2.37–2.25 (1H, m), 1.09 (9H, s), 1.08 (3H, d, *J* = 6.5 Hz), 1.00 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 177.6 (C), 170.2 (C), 159.7 (C), 134.1 (CH), 129.7 (C), 129.5 (CH), 117.0 (CH_2), 113.5 (CH), 80.6 (CH), 73.1 (CH), 71.7 (CH), 69.2 (CH_2), 55.2 (CH_3), 38.4 (C), 30.6 (CH), 30.4 (CH_2), 26.8 (CH_3), 19.1 (CH_3), 17.7 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OC_3H_5]^+$ $C_{21}H_{28}NO_4S_2$: 422.1454, found: 422.1442; *m/z* calcd for $[M+Na]^+$ $C_{24}H_{33}NNaO_5S_2$: 502.1692, found: 502.1687.

(*S*)-*N*-[(2*R*,3*R*)-3-Benzyloxy-3-(4-methoxyphenyl)-2-pivaloyloxypropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (14n): The reaction was carried out as described in General Procedure using $(Me_3P)_2NiCl_2$ (3.5 mg, 12.5 μmol, 2.5 mol%), **7** (152 mg, 0.5 mmol), 4-methoxybenzaldehyde dibenzyl acetal (**n**, 184 mg, 0.55 mmol), and TESOTf (130 μL, 0.58 mmol). The crude was purified by column chromatography (hexanes/EtOAc 90:10) to give 183 mg (0.35 mmol, 69% yield) of **14n** as a yellow oil. R_f (hexanes/EtOAc 90:10) = 0.40. $[\alpha]_D^{20}$ = +137.5 (*c* = 1.00, $CHCl_3$). IR (ATR) ν = 2962, 2870, 1724, 1690, 1605, 1509, 1357, 1249, 1171, 1142 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.44–7.42 (2H, m), 7.30–7.21 (5H, m), 7.04 (1H, d, *J* = 7.1 Hz), 6.91–6.87 (2H, m), 5.19 (1H, ddd, *J* = 8.2, 5.9, 0.8 Hz), 4.88 (1H, d, *J* = 7.1 Hz), 4.46 (1H, d, *J* = 12.1 Hz), 4.25 (1H, d, *J* = 12.1 Hz), 3.81 (3H, s), 3.57 (1H, dd, *J* = 11.4, 8.2 Hz), 2.96 (1H, dd, *J* = 11.4, 0.8 Hz), 2.25–2.14 (1H, m), 1.10 (9H, s), 0.91 (3H, d, *J* = 6.8 Hz), 0.88 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 202.6 (C), 177.6 (C), 169.8 (C), 159.7 (C), 137.7 (C), 129.6 (CH), 129.3 (C), 128.0 (CH), 127.4 (CH), 127.3 (CH), 113.5 (CH), 80.9 (CH), 73.2 (CH), 71.6 (CH), 70.3 (CH_2), 55.2 (CH_3), 38.3 (C), 30.6 (CH), 30.4 (CH_2), 26.8 (CH_3), 18.9 (CH_3), 17.3 (CH_3). HRMS (+ESI): *m/z* calcd for $[M–OBn]^+$ $C_{21}H_{28}NO_4S_2$: 422.1454, found: 422.1447; *m/z* calcd for $[M+Na]^+$ $C_{28}H_{35}NNaO_5$.

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[20] As established in preceding studies (see ref. 17), TMSOTf, TBSOTf, or TIPSOTf can also be also used, but these Lewis acids provide slightly poorer yields and stereocontrol.

[21] Acetals **a** and **e** are commercially available. The others are prepared from the corresponding aldehydes according to common methods.

[22] Comparison of the physical and spectroscopic data of **14e** and **14g** with those reported in the literature (see ref. 16) confirmed the *anti* configuration of glycolate adducts **14**.

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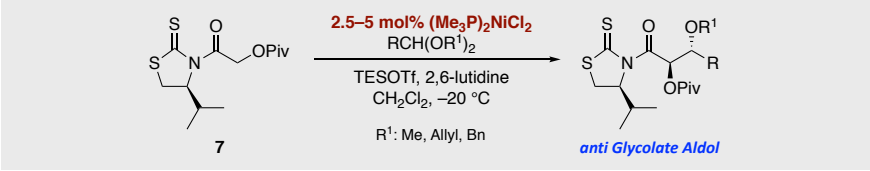
Layout 2:

FULL PAPER



Tiny amounts of commercially available and easy to handle $(Me_3P)_2NiCl_2$ trigger the stereoselective aldol addition of chiral *N*-2-pivaloyloxyacetyl thiazolidinethione **7** to acetals to provide the corresponding *anti* glycolate adducts in a highly efficient manner

Stereoselective Synthesis

Juan Manuel Romo, Pedro Romea, and Fèlix Urpí**

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Direct *anti* Glycolate Aldol Reaction of Protected Chiral *N*-Hydroxyacetyl Thiazolidinethiones with Acetals Catalyzed by a Nickel(II) Complex