2,5-Dihydro-1,3-thiazoles as Scaffolds in the Synthesis of *O*,*N*-Diacyl *O*,*N*-Acetals in a One-pot Reaction

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Dedicated to Professor Heribert Offermanns on the occasion of his 75th birthday

The Asinger reaction is a very powerful tool to form 2,5-dihydro-1,3-thiazoles in high yields. Treating these heterocyclic imines with acid chlorides followed by adding sodium carboxylates led to a large number of new *O*,*N*-diacyl *O*,*N*-acetals. Using chiral starting materials, a high diastereoselectivity was observed in several cases. X-Ray structures document the constitution and clarify the relative configuration of the prepared *O*,*N*-diacyl *O*,*N*-acetals.

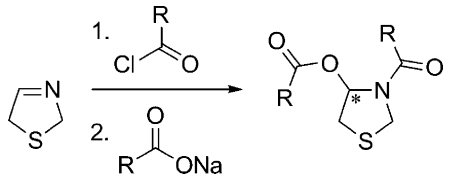
Key words: Imines, Acetals, *N*-Acyliminium Ion, Carboxylates, Stereochemistry

Introduction

For more than 60 years the chemistry of 2,5-dihydro-1,3-thiazoles is a key element in the course of developing pharmaceutically active molecules [1]. Several processes based on this reactive class of substances are still in progress represented by the synthesis of penicillamine and cysteine [2, 3]. Furthermore, other remarkable investigations on this family of heterocycles and its related biological useful structure elements characterize special fields of research in general [4]. The synthesis of 2,5-dihydro-1,3-thiazoles, which belong to the class of cyclic imines, was first reported by F. Asinger in 1956 [5]. The Asinger reaction is a multi-component reaction (MCR) of two molecules of one ketone, bearing a proton in α-position, with ammonia and sulfur forming 2,5-dihydro-1,3-thiazoles. Till this day the Asinger four-component reaction (A-4CR) has been optimized more and more, ending in the most efficient and elegant access to these heterocycles: the modified Asinger reaction [3]. Laying the foundation of this reaction in the environment of Asinger, the modified Asinger reaction was accomplished by H. Offermanns amongst others [3]. The modified Asinger reaction established the possibility of a higher diversity of products due to the formation of a 2,5-dihydrothiazole starting from two completely different carbonyl compounds in a one-pot reaction. For that purpose, one of the carbonyl compounds has to be transformed into an α-chlorocarbonyl compound. Furthermore, the modified Asinger reaction is more feasible by reason of the abstinence from gaseous ammonia and elemental sulfur. Instead, the mentioned α-chlorocarbonyl compound reacts with sodium hydrogen sulfide generating *in situ* thiols, which undergo directly a reaction with the two remaining reagents.

2,5-Dihydro-1,3-thiazoles could be converted into a large number of different products by functionalizing their reactive C=N double bond [6 – 10]. Accordingly, we were successful in generating different types of amide structures, especially enantio- or diastereospecifically formed products [11 – 18]. However, the derivatizations often had to be initiated by the addition of an acid chloride generating reactive chloroamides [19 – 24]. These intermediates were quenched directly with different hydroxy compounds to prepare stable alkoxyamides.

Considering the vast number of *O*,*N*-diacyl *O*,*N*-acetals and their diverse applications [25 – 28], subject



Scheme 1. One-pot synthesis of *O*,*N*-diacyl *O*,*N*-acetals starting from 2,5-dihydro-1,3-thiazoles.

of the present study is a synthesis route which enables the preparation of new *O*,*N*-diacyl *O*,*N*-acetals starting from 2,5-dihydro-1,3-thiazoles in a one-pot synthesis (Scheme 1).

Treatment of the 2,5-dihydro-1,3-thiazoles with various acid chlorides followed by the addition of sodium carboxylates led to the target *O*,*N*-diacyl *O*,*N*-acetals. Additionally, we investigated the diastereoselectivity of this reaction by varying the substituents at the thiazole ring and applying a diverse series of acid chlorides and sodium salts.

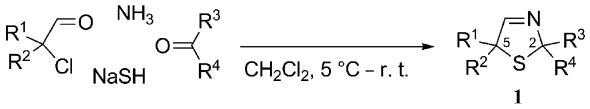
However, this efficient synthesis route to *O*,*N*-diacyl *O*,*N*-acetals has attracted limited attention [29, 30], whereas the synthesis by esterification of the respective hydroxy species with acetic anhydride is a commonly used method [31 – 34]. It is worth mentioning that the second described pathway implies a complex and protracted two-step sequence compared to the investigated procedure based on imines.

Results and Discussion

Synthesis of 2,5-dihydro-1,3-thiazoles

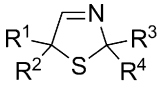
By means of the modified Asinger reaction [3] four different 2,5-dihydro-1,3-thiazoles **1** were prepared as precursors for the intended route. The synthesis was realized by using an α-chloroaldehyde, a second variable carbonyl compound (aldehyde or ketone), aqueous ammonia and sodium hydrogen sulfide in dichloromethane (Scheme 2).

In addition to the established cyclic imines **1a**–**b** and **1d**, we report on compound **1c** for the first time. As



Scheme 2. Synthesis of the 2,5-dihydro-1,3-thiazoles **1** (R^1, R^2 = alkyl, aryl; R^3, R^4 = H, alkyl) [3].

Table 1. Prepared 2,5-dihydro-1,3-thiazoles **1**.



1

Imine	R^1	R^2	R^3	R^4	Yield[a] (%)
1a	CH_3	CH_3	CH_3	CH_3	88 [35]
1b	CH_3	CH_3	-$(CH_2)_5$-		65 [36]
1c	CH_3	C_6H_5	CH_3	CH_3	58
1d	CH_3	CH_3	H	$C(CH_3)_3$	89 [37]

[a] All yields are isolated yields.

expected, the desired 2,5-dihydro-1,3-thiazoles **1** were obtained in good yields (up to 89 %) (Table 1).

In order to gain chiral starting materials for the reactions, different substituents of the carbonyl compounds were chosen. This approach offers the possibility to investigate the diastereoselectivity of C2- as well as C5-chiral imines **1**.

Conversion of the 2,5-dihydro-1,3-thiazoles into O,N-diacyl O,N-acetals

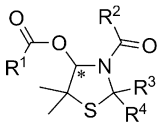
Among the most efficient possibilities to take advantage of the reactive imine bond of the 2,5-dihydro-1,3-thiazoles **1** is the addition of an acyl chloride [19 – 24].

As outlined in Scheme 3, firstly, the imines **1** were reacted with several acyl chlorides in acetonitrile to generate chloroamides which are in equilibrium with reactive *N*-acyliminium ions. These intermediates were then quenched directly with the sodium salts of different carboxylic acids. The *O*,*N*-diacyl *O*,*N*-acetals **2**, **3** and **4** were smoothly obtained in moderate to good yields *via* that nucleophilic substitution (Tables 2, 3 and 4).

Starting from the imines **1a** and **1b** the *O*,*N*-diacyl *O*,*N*-acetals **2** were obtained as racemates after workup by column chromatography or recrystallization (Table 2). The results demonstrate the variability of the acyl chloride and the carboxylic acid. Most notably, a high conversion could be reached by using sodium benzoate as nucleophile. Accordingly, the *O*,*N*-diacyl *O*,*N*-acetal **2f** was obtained in 87 % yield. Even if the yield was only moderate, the synthesis of formic ester (**2e**) was also possible.

Apart from the 2,5-dihydro-1,3-thiazoles **1a** and **1b**, the imines **1c** and **1d** were converted to the *O*,*N*-diacyl *O*,*N*-acetals **3** and **4** *via* the described synthesis route. The characteristic attribute of the 2,5-dihydro-

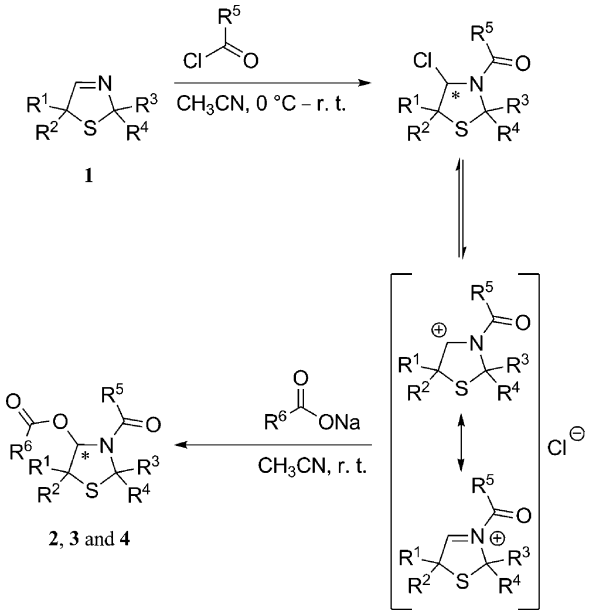
Table 2. Racemic *O*,*N*-diacyl *O*,*N*-acetals **2** containing one stereogenic center[a].



2

Imine	*O*,*N*-Acetal	R^1	R^2	R^3	R^4	Yield[b] (%)
1a	**2a**	CH_3	C_6H_5	CH_3	CH_3	72
1a	**2b**	CH_3	CH_3	CH_3	CH_3	69
1a	**2c**	CH_3	C_2H_5	CH_3	CH_3	55
1a	**2d**	CH_3	*trans*-CH=CHC_6H_5	CH_3	CH_3	63
1a	**2e**	H	C_6H_5	CH_3	CH_3	43
1a	**2f**	C_6H_5	CH_3	CH_3	CH_3	87
1b	**2g**	CH_3	*trans*-CH=CHC_6H_5	-$(CH_2)_5$-		76

[a] All reactions were performed with an imine-acyl chloride-sodium carboxylate ratio of 1 : 1.1 : 4; [b] all yields are isolated yields.

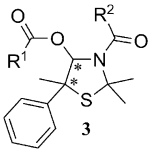


Scheme 3. One-pot synthesis of the *O*,*N*-diacyl *O*,*N*-acetals **2**, **3** and **4** (R^1, R^2 = alkyl, aryl; R^3, R^4 = H, alkyl; R^5 = alkyl, aryl, aralkenyl; R^6 = H, alkyl, aryl).

1,3-thiazoles **1c** and **1d** is their stereogenic center. Generating the *O*,*N*-diacyl *O*,*N*-acetals **3** and **4** starting from the racemic imines **1c** and **1d** led to the formation of two racemic diastereomers (Tables 3 and 4). Due attention needs to be paid to the fact that the configuration at the existing stereogenic center of the imines can influence the formation of the new chirality center formed in the reaction [18, 38].

All *O*,*N*-diacyl *O*,*N*-acetals (**3** and **4**) were obtained in moderate to very good yields. The use of sodium

Table 3. Racemic *O*,*N*-diacyl *O*,*N*-acetals **3** containing two stereogenic centers[a].

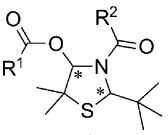


3

Imine	*O*,*N*-Acetal	R^1	R^2	Yield[b] (%)	*dr*[c]
1c	**3a**	CH_3	C_6H_5	65	87 : 13
1c	**3b**	H	C_6H_5	60	61 : 39
1c	**3c**	C_6H_5	CH_3	84	76 : 24
1c	**3d**	H	CH_3	62	85 : 15

[a] All reactions were performed with an imine-acyl chloride-sodium carboxylate ratio of 1 : 1.1 : 4; [b] all yields are isolated total yields; [c] diastereomeric ratio according to the ^{1}H NMR spectrum of the crude product.

Table 4. Racemic *O*,*N*-diacyl *O*,*N*-acetals **4** containing two stereogenic centers[a].



4

Imine	*O*,*N*-Acetal	R^1	R^2	Yield[b] (%)	*dr*[c]
1d	**4a**	CH_3	C_6H_5	55	71 : 29
1d	**4b**	H	C_6H_5	78	65 : 35
1d	**4c**	C_6H_5	CH_3	80	92 : 8
1d	**4d**	H	CH_3	77	90 : 10
1d	**4e**	CH_3	CH_3	72	> 95 : 5
1d	**4f**	CH_3	*trans*-CH=CHC_6H_5	83	74 : 26

[a] All reactions were performed with an imine-acyl chloride-sodium carboxylate ratio of 1 : 1.1 : 4; [b] all yields are isolated total yields; [c] diastereomeric ratio according to the ^{1}H NMR spectrum of the crude product.

benzoate in the synthesis of **3c** and **4c** led to yields similar to that of the formation of **2f** (see above). The mentioned influence of the configuration at the existing stereogenic center of the imines on the stereochemical course of the reaction causes a diastereoselective formation of the products **3** and **4**. In one case the *O*,*N*-diacyl *O*,*N*-acetal was even formed diastereospecifically (**4e**). On the whole, no crucial difference between the diastereoselectivities of the formations of the *O*,*N*-diacyl *O*,*N*-acetals **3** and **4** could be noticed, although the highest diastereoselectivities were obtained starting from the imine **1d**.

We were able to obtain single crystals of the major diastereomer of **3a** and **4e** to verify the proposed structures by single-crystal X-ray diffraction analysis (Figs. 1 and 2). Additionally, the relative configuration of the two stereocenters was determined.

The structure of the major diastereomer of **3a** documents the expected *trans*-configuration between the carboxyl and the phenyl group (Fig. 1). In contrast, a *cis*-configuration between the carboxyl group and the *tert*-butyl group has been revealed by the X-ray crystal structure of the major diastereomer of **4e** (Fig. 2). In compliance with the NMR data, the relative configuration of all *O*,*N*-diacyl *O*,*N*-acetals **3** and **4** were appointed congruent to the configurations documented by the X-ray crystal structure analyses of **3a** and **4e**. That circumstance points out the different influences of the existing stereogenic center of the imines on the creation of the new chiral center.

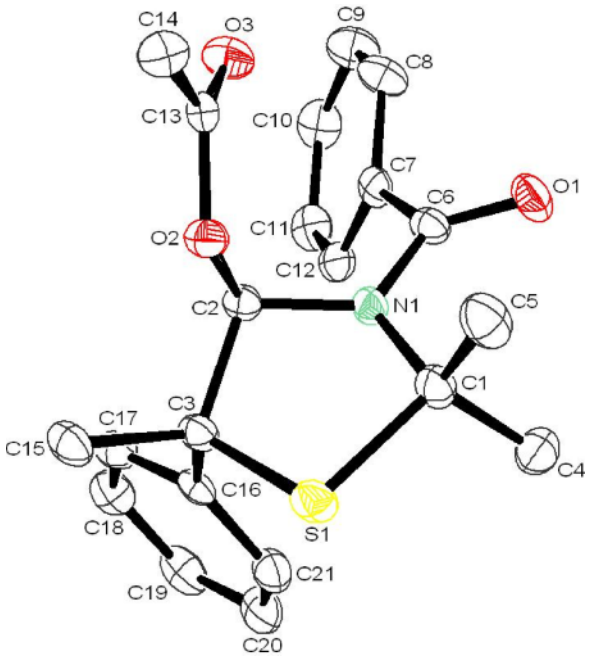


Fig. 1 (color online). Molecular structure of the major diastereomer (*R**,*R**)-**3a** in the crystal. The crystallographic atom numbering does not follow the IUPAC nomenclature.

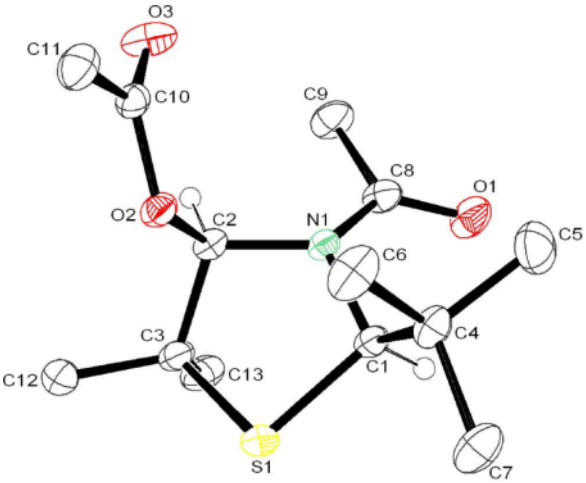


Fig. 2 (color online). Molecular structure of the major diastereomer (*R**,*R**)-**4e** in the crystal. The crystallographic atom numbering does not follow the IUPAC nomenclature.

As shown in Fig. 3, the *N*-acyliminium ions leading to the amides **3** are attacked by the carboxylate *trans* to the phenyl group. The reason for this reaction course is the bulkiness of the phenyl group. The likewise voluminous carboxylate avoids the bulky phenyl group [18, 38] and attacks from the less hindered side resulting predominantly in *trans*-configurated amides **3**. On the other hand, the attack of the carboxylate on the *N*-acyliminium ions occurs *cis* to the *tert*-butyl group during the reaction to *O*,*N*-diacyl *O*,*N*-acetals **4** (Fig. 4). In that case the existing stereogenic cen-

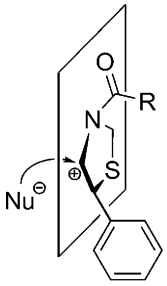


Fig. 3. Preferred attack of the carboxylate leading to *trans*-configurated *O*,*N*-diacyl *O*,*N*-acetals **3**. For the sake of clarity, the methyl groups are omitted.

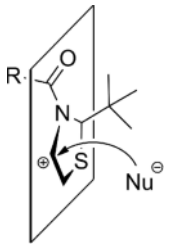


Fig. 4. Preferred attack of the carboxylate leading to *cis*-configurated *O*,*N*-diacyl *O*,*N*-acetals **4**. For the sake of clarity, the methyl groups are omitted.

ter is further away from the reaction center. On account of this, the direct influence on the creation of the new stereogenic center is less important. In fact, the bulky *tert*-butyl group displaces the amido moiety to the opposite site [18, 38]. The attack of the carboxylate occurs, therefore, evasively on the amido moiety leading predominantly to *cis*-configurated *O*,*N*-diacyl *O*,*N*-acetals **4**.

Conclusion

Starting from different achiral and chiral 2,5-dihydro-1,3-thiazoles **1**, which were obtained by the modified Asinger reaction, we succeeded in the synthesis of the new *O*,*N*-diacyl *O*,*N*-acetals **2**, **3** and **4** in moderate to very good yields in a one-pot reaction. With C2-chiral as well as C5-chiral starting materials we observed high diastereoselectivity in certain cases. All relative configurations were clarified by X-ray crystal structure analyses. The presented study has opened new routes to *O*,*N*-diacyl *O*,*N*-acetals based on 2,5-dihydro-1,3-thiazoles and similar heterocycles which are known for the pharmacological relevance of their structural elements.

Experimental Section

Preparative column chromatography was carried out using Grace SiO_2 (0.035 – 0.070 mm, type KG 60) with *n*-hexane and ethyl acetate as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminum sheets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 500 instrument. Multiplicities of carbon signals were determined with DEPT experiments. Assignments of proton and carbon resonances were made with H,H-COSY and HMQC experiments. MS and HRMS spectra were obtained with a Finnigan MAT 95 (EI and CI) and a Waters Q-TOF Premier (ESI, positive mode) spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond ATR unit. The following starting materials were prepared by literature procedures: cinnamoyl chloride [39], 2-chloro-2-methylpropanal [40] and (*RS*)-2-chloro-2-phenylpropanal [41]. The sodium carboxylates were dried in vacuum by heating to 200 °C in the presence of Sicapent®. All other starting materials were commercially available and used without further purification. In cases of diastereomeric products (**3a–d** and **4a–f**), only the major one is described.

*2,2,5,5-Tetramethyl-2,5-dihydrothiazole (**1a**)* [35]

To a suspension of sodium hydrogen sulfide hydrate (26.66 g, 0.36 mol), acetone (57.93 g, 1.00 mol) and 25 % aqueous ammonia solution (60.66 g, 0.91 mol) 2-chloro-2-methylpropanal (35.66 g, 0.34 mol) was added dropwise while the temperature was kept between 5 °C and 10 °C. Afterwards the suspension was warmed to room temperature, and 133 mL of dichloromethane was added. The resulting reaction mixture was stirred for 2 h at room temperature. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed at the rotary evaporator. The residue was recrystallized from petroleum ether 40/60. The title compound was obtained as a colorless solid (41.94 g, 0.29 mol, 88 %). M. p. 51 °C. – ^{1}H NMR (125.8 MHz, $CDCl_3$): $\delta = 1.56$, 1.68 (2s, 12H, 2 × C(CH_3)$_2$), 6.84 (s, 1H, CH) ppm. – ^{13}C NMR (500.1 MHz, $CDCl_3$): $\delta = 29.9$, 33.7 (2 × C(CH_3)$_2$), 65.5 (*C*(CH_3)$_2$), 89.2 (*C*(CH_3)$_2$), 165.7 (C=N) ppm.

*2,2-Dimethyl-1-thia-4-azaspiro[4.5]dec-3-ene (**1b**)* [36]

To a suspension of sodium hydrogen sulfide hydrate (22.40 g, 0.30 mol), cyclohexanone (29.50 g, 0.30 mol) and 25 % aqueous ammonia solution (16.95 g, 0.32 mol) 2-chloro-2-methylpropanal (21.33 g, 0.20 mol) was added dropwise while the temperature was kept between 5 °C and 10 °C. Afterwards the suspension was warmed to room temperature and 50 mL of dichloromethane was added. The resulting reaction mixture was stirred for 15 h at room temperature. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed at the rotary evaporator. The crude product was purified by fractional distillation (76 °C, 1 mbar). The title compound was obtained as a colorless oil (24.18 g, 0.13 mol, 65 %). B. p. 76 °C/1 mbar. – ^{1}H NMR (125.8 MHz, $CDCl_3$): $\delta = 1.24 – 1.50$, 1.52 – 2.06 (2m, 10H, -(CH_2)$_5$-), 1.51 (s, 6H, C(CH_3)$_2$), 6.94 (s, 1H, CH) ppm. – ^{13}C NMR (500.1 MHz, $CDCl_3$): $\delta = 24.1$ (C(*C*H_3)$_2$), 24.8, 30.1, 42.1 (-(CH_2)$_5$-), 62.7 (*C*(CH_3)$_2$), 95.7 (*C*-(CH_2)$_5$-), 165.6 (C=N) ppm.

*(RS)-2,2,5-Trimethyl-5-phenyl-2,5-dihydrothiazole (**1c**)*

To a suspension of sodium hydrogen sulfide hydrate (27.91 g, 0.38 mol), acetone (47.00 g, 0.81 mol) and 25 % aqueous ammonia solution (50.05 g, 0.95 mol) (*RS*)-2-chloro-2-phenylpropanal (64.31 g, 0.38 mol) was added dropwise while the temperature was kept between 5 °C and 10 °C. Afterwards again 25 % aqueous ammonia solution (9.10 g, 0.14 mol) and 10 mL of dichloromethane were added. The resulting reaction mixture was stirred for 15 h at 10 °C. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed at the rotary evaporator. The crude product was purified by fractional distillation (90 – 92 °C, 0.65 mbar). The title compound was obtained as a yellow oil (45.19 g, 0.22 mol, 58 %). B. p. 90 – 92 °C/0.65 mbar. – IR (ATR): ν = 2973, 2926, 1647, 1445, 1363, 1127, 932, 760, 697 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.73, 1.75 (2s, 6H, $C(CH_3)_2$), 1.95 (s, 3H, CCH_3), 7.08 (s, 1H, CH), 7.20 – 7.39 (m, 5H, CH^{Ar}) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 28.6 (CCH_3), 32.9, 33.6 ($C(CH_3)_2$), 71.6 (CCH_3), 89.7 ($C(CH_3)_2$), 126.3, 127.3, 128.6, 143.3 (C^{Ar}), 163.0 (C=N) ppm. – MS (CI, isobutane): m/z (%) = 206.2 (100) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 206.0998 (calcd. 206.1003 for $C_{12}H_{16}NS$, $[M+H]^+$).

*(RS)-2-tert-Butyl-5,5-dimethyl-2,5-dihydrothiazole (**1d**) [37]*

To a suspension of sodium hydrogen sulfide hydrate (20.35 g, 0.27 mol), pivalaldehyde (25.75 g, 0.30 mol) and 25 % aqueous ammonia solution (38.68 g, 0.58 mol) 2-chloro-2-methylpropanal (26.63 g, 0.25 mol) was added dropwise while the temperature was kept between 5 °C and 10 °C. The resulting reaction mixture was stirred for 3 h at room temperature. Afterwards 100 mL of dichloromethane was added to the suspension. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed at the rotary evaporator. The crude product was purified by fractional distillation (59 °C, 1.33 mbar). The title compound was obtained as a colorless oil (38.03 g, 0.22 mol, 89 %). B. p. 59 °C/1.33 mbar. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.95 (s, 9H, $C(CH_3)_3$), 1.45 (s, 6H, $C(CH_3)_2$), 5.51 (d, ^4J = 2.5 Hz, 1H, $CHC(CH_3)_3$), 6.98 (d, ^4J = 2.5 Hz, 1H, CH) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.7 ($C(CH_3)_3$), 29.0, 29.7 ($C(CH_3)_2$), 36.0 ($C(CH_3)_3$), 63.5 ($C(CH_3)_2$), 95.2 ($CHC(CH_3)_3$), 168.5 (C=N) ppm.

*General Procedure (GP) for the synthesis of the O,N-diacyl O,N-acetals **2**, **3** and **4***

Under argon atmosphere one equivalent of the respective 2,5-dihydrothiazole dissolved in anhydrous acetonitrile was cooled to 0 – 5 °C before 1.1 equivalents of the acyl chloride was added dropwise. After stirring for 16 h at room temperature four equivalents of the respective dried sodium carboxylate were added. After stirring for 16 h at room temperature the solvent was removed at the rotary evaporator. The residue was extracted with 100 mL of *n*-hexane-dichloromethane (1:1) and filtered. The solvent was removed at the rotary evaporator. The purification of the crude product is described in the individual experimental details.

*(RS)-3-Benzoyl-2,2,5,5-tetramethyl-1,3-thiazolidin-4-yl acetate (**2a**)*

Following the GP, dihydrothiazole **1a** (2.86 g, 19.97 mmol), benzoyl chloride (3.09 g, 21.98 mmol) and sodium acetate (6.56 g, 79.97 mmol) were used. The crude product was crystallized from petroleum ether 40/60. The title compound was obtained as a colorless solid (4.42 g, 14.38 mmol, 72 %). M. p. 123 °C. – IR (ATR): ν = 2974, 2935, 1735, 1664 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.20, 1.65, 1.98, 2.00 (4s, 12H, 2 × $C(CH_3)_2$), 2.05 ($COCH_3$), 6.27 (s, 1H, CH), 7.31 – 7.40 (m, 5H, CH^{Ar}) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 20.6 ($COCH_3$), 23.0, 30.8, 30.9 (2 × $C(CH_3)_2$), 52.2 ($C(CH_3)_2$), 73.0 ($C(CH_3)_2$), 93.5 (CH), 125.6, 126.3, 128.3, 128.6, 129.8, 137.5 (C^{Ar}), 168.9, 170.7 (2 × CO) ppm. – MS (CI, isobutane): m/z (%) = 308.1 (100) $[M+H]^+$. – HRMS (EI, 70 eV): m/z = 307.1243 (calcd. 307.1242 for $C_{16}H_{21}NO_3S$, $[M]^+$).

*(RS)-3-Acetyl-2,2,5,5-tetramethyl-1,3-thiazolidin-4-yl acetate (**2b**)*

Following the GP, dihydrothiazole **1a** (2.86 g, 19.97 mmol), acetyl chloride (1.71 g, 21.79 mmol) and sodium acetate (6.56 g, 79.97 mmol) were used. The crude product was crystallized from diethyl ether. The title compound was obtained as a colorless solid (3.38 g, 13.78 mmol, 69 %). M. p. 43 °C. – IR (ATR): ν = 2983, 1674, 1340, 1212 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.25, 1.55, 1.79, 1.91 (4s, 12H, 2 × $C(CH_3)_2$), 2.11 (s, 3H, $OCOCH_3$), 2.20 (s, 3H, $NCOCH_3$), 6.40 (s, 1H, CH) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 20.8, 23.0 (2 × $COCH_3$), 26.1, 29.9, 30.4, 31.8 (2 × $C(CH_3)_2$), 51.8 ($C(CH_3)_2$), 68.5 ($C(CH_3)_2$), 92.6 (CH), 169.6, 170.2 (2 × CO) ppm. – MS (CI, isobutane): m/z (%) = 246.2 (100) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 246.1163 (calcd. 246.1164 for $C_{11}H_{20}NO_3S$, $[M+H]^+$).

*(RS)-3-Propanoyl-2,2,5,5-tetramethyl-1,3-thiazolidin-4-yl acetate (**2c**)*

Following the GP, dihydrothiazole **1a** (1.43 g, 9.98 mmol), propanoyl chloride (1.01 g, 10.92 mmol) and sodium acetate (3.28 g, 39.99 mmol) were used. The

crude product was crystallized from diethyl ether. The title compound was obtained as a colorless solid (1.42 g, 5.47 mmol, 55 %). M. p. 42 °C. – IR (ATR): $\nu = 2974, 2939, 1727, 1677, 1354, 1218\,cm^{-1}$. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.14$ (t, $^3J = 7.9$ Hz, 3H, CH_2CH_3), 1.35, 1.53, 1.80, 1.91 (4s, 12H, $2 \times C(CH_3)_2$), 2.08 (s, 3H, $COCH_3$), 2.46 (q, $^3J = 7.9$ Hz, 2H, CH_2CH_3), 6.49 (s, 1H, CH) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 9.07$ (CH_2CH_3), 20.5 ($COCH_3$), 23.1, 29.5, 29.8, 23.8 ($2 \times C(CH_3)_2$), 26.9 (CH_2CH_3), 53.2 ($C(CH_3)_2$), 68.5 ($C(CH_3)_2$), 101.5 (CH), 169.1, 173.4 ($2 \times$ CO) ppm. – MS (CI, isobutane): m/z (%) = 260.2 (100) $[M+H]^+$. – HRMS (CI, isobutane): $m/z = 260.1321$ (calcd. 260.1320 for $C_{12}H_{22}NO_3S$, $[M+H]^+$).

*(RS)-2,2,5,5-Tetramethyl-3-[(2E)-3-phenylprop-2-enoyl]-1,3-thiazolidin-4-yl acetate (**2d**)*

Following the GP, dihydrothiazole **1a** (2.86 g, 19.97 mmol), cinnamoyl chloride (3.66 g, 21.97 mmol) and sodium acetate (6.56 g, 79.97 mmol) were used. The crude product was purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 3 : 2, $R_f = 0.80$). The title compound was obtained as a colorless solid (4.20 g, 12.60 mmol, 63 %). M. p. 149 °C. – IR (ATR): $\nu = 2995, 2977, 2932, 1718, 1668, 740\,cm^{-1}$. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.40, 1.57, 1.88, 2.02$ (4s, 12H, $2 \times C(CH_3)_2$), 2.09 (s, 3H, $COCH_3$), 6.76 (s, 1H, NCH), 6.96 (d, $^3J = 15.4$ Hz, 1H, C*H*=CHPh), 7.30 – 7.50 (m, 5H, CH^{Ar}), 7.68 (d, $^3J = 15.4$ Hz, 1H, CH=C*H*Ph) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 20.4$ ($COCH_3$), 23.9, 29.8, 29.9, 30.7 ($2 \times C(CH_3)_2$), 51.8 ($C(CH_3)_2$), 73.9 ($C(CH_3)_2$), 91.4 (NCH), 118.7 (*C*H=CHPh), 127.9, 128.0, 128.7, 128.8, 129.7, 135.0 (C^{Ar}), 144.3 (CH=*C*HPh), 165.5, 170.4 ($2 \times$ CO) ppm. – MS (CI, isobutane): m/z (%) = 334.2 (100) $[M+H]^+$. – HRMS (CI, isobutane): $m/z = 334.1476$ (calcd. 334.1477 for $C_{18}H_{24}NO_3S$, $[M+H]^+$).

*(RS)-3-Benzoyl-2,2,5,5-tetramethyl-1,3-thiazolidin-4-yl formate (**2e**)*

Following the GP, dihydrothiazole **1a** (1.43 g, 9.98 mmol), benzoyl chloride (1.55 g, 11.03 mmol) and sodium formate (2.72 g, 40.00 mmol) were used. The crude product was purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 1 : 1, $R_f = 0.86$). The title compound was obtained as a colorless solid (1.25 g, 4.26 mmol, 43 %). M. p. 113 – 116 °C. – IR (ATR): $\nu = 2976, 2931, 1718, 1661, 1444, 1068, 698\,cm^{-1}$. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.20, 1.65, 2.05, 2.10$ (4s, 12H, $2 \times C(CH_3)_2$), 6.45 (s, 1H, CH), 7.19–8.01 (m, 5H, CH^{Ar}), 7.91 (s, 1H, CHO) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 23.2, 30.9, 31.1, 31.6$ ($2 \times C(CH_3)_2$), 52.7 ($C(CH_3)_2$), 73.0 ($C(CH_3)_2$), 94.1 (CH), 125.6, 128.5, 128.6, 129.1, 129.6, 137.5 (C^{Ar}), 164.5 (CO), 170.0 (CHO) ppm. – MS (CI, isobutane): m/z (%) = 294.1 (100) $[M+H]^+$. – HRMS (CI, isobutane): $m/z = 294.1163$ (calcd. 294.1164 for $C_{15}H_{20}NO_3S$, $[M+H]^+$).

*(RS)-3-Acetyl-2,2,5,5-tetramethyl-1,3-thiazolidin-4-yl benzoate (**2f**)*

Following the GP, dihydrothiazole **1a** (2.86 g, 19.97 mmol), acetyl chloride (1.71 g, 21.79 mmol) and sodium benzoate (11.52 g, 79.94 mmol) were used. The crude product was purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 4 : 1, $R_f = 0.48$). The title compound was obtained as a colorless oil (5.34 g, 17.37 mmol, 87 %). – IR (ATR): $\nu = 2986, 2929, 1748, 1344, 1211, 705\,cm^{-1}$. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.26, 1.59, 1.88, 1.94$ (4s, 12H, $2 \times C(CH_3)_2$), 2.14 (s, 3H, $COCH_3$), 6.64 (s, 1H, CH), 7.38–8.11 (m, 5H, CH^{Ar}) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 21.5, 21.3, 22.9, 29.8, 30.7$ ($5 \times CH_3$), 54.8 ($C(CH_3)_2$), 73.6 ($C(CH_3)_2$), 91.7 (CH), 123.5, 124.7, 126.9, 128.7, 128.8, 135.8 (C^{Ar}), 167.8, 171.7 ($2 \times$ CO) ppm. – MS (CI, isobutane): m/z (%) = 308.0 (100) $[M+H]^+$. – HRMS (CI, isobutane): $m/z = 308.1315$ (calcd. 308.1320 for $C_{16}H_{22}NO_3S$, $[M+H]^+$).

*(RS)-2,2-Dimethyl-4-[(2E)-3-phenylprop-2-enoyl]-1-thia-4-azaspiro[4.5]decan-3-yl acetate (**2g**)*

Following the GP, dihydrothiazole **1b** (3.66 g, 19.97 mmol), cinnamoyl chloride (3.66 g, 21.79 mmol) and sodium acetate (6.56 g, 79.97 mmol) were used. The crude product was purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 9 : 1, $R_f = 0.37$). The title compound was obtained as a colorless solid (5.67 g, 15.18 mmol, 76 %). M. p. 124 – 125 °C. – IR (ATR): $\nu = 2991, 2933, 1730, 1658, 1449, 1193, 731\,cm^{-1}$. – ^1H NMR (500.1 MHz, $CDCl_3$): $\delta = 1.20 - 1.38$, 1.53 – 1.90, 2.82 – 3.25 (3m, 10H, -$(CH_2)_5$-), 1.40, 1.52 (2s, 6H, $C(CH_3)_2$), 2.09 (s, 3H, $COCH_3$), 6.78 (s, 1H, NCH), 6.96 (d, $^3J = 15.5$ Hz, 1H, C*H*=CHPh), 7.34 – 7.54 (m, 5H, CH^{Ar}), 7.65 (d, $^3J = 15.5$ Hz, 1H, CH=C*H*Ph) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 20.4$ ($COCH_3$), 24.1, 24.4 ($C(CH_3)_2$), 25.1, 25.3, 25.4, 25.8, 30.0 (-$(CH_2)_5$-), 51.0 ($C(CH_3)_2$), 80.2 (*C*-$(CH_2)_5$-), 92.2 (NCH), 119.5 (*C*H=CHPh), 127.9, 128.0, 128.7, 128.8, 129.7, 135.0 (C^{Ar}), 142.8 (CH=*C*HPh), 165.8, 170.5 ($2 \times$ CO) ppm. – MS (ESI): m/z (%) = 395.9 (100) $[M+Na]^+$. – HRMS (ESI): $m/z = 395.9245$ (calcd. 395.9245 for $C_{21}H_{27}NNaO_3S$, $[M+Na]^+$).

(4R,5R*)-3-Benzoyl-2,2,5-trimethyl-5-phenyl-1,3-thiazolidin-4-yl acetate (**3a**)*

Following the GP, dihydrothiazole **1c** (2.05 g, 9.98 mmol), benzoyl chloride (1.55 g, 10.76 mmol)

and sodium acetate (3.28 g, 39.99 mmol) were used. A mixture of both racemic diastereomers was obtained as the crude product (2.40 g, 6.49 mmol, 65 %, *dr* = 87:13). For analysis, the racemic diastereomers were crystallized from *n*-hexane to give the major racemic diastereomer as a colorless solid. M. p. 89 – 94 °C. – IR (ATR): ν = 3065, 2986, 2927, 1741, 1656, 1358, 1208, 698 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.47, 1.87 (2s, 6H, $C(CH_3)_2$), 2.05 (s, 3H, CCH_3), 2.08 (s, 3H, $COCH_3$), 6.90 – 6.91 (m, 2H, CH^{Ar}), 6.92 (s, 1H, CH), 7.27 – 7.73 (m, 8H, CH^{Ar}) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 20.8 ($CO\mathit{C}H_3$), 26.3, 29.8, 30.7 ($C(\mathit{C}H_3)_2$, $C\mathit{C}H_3$), 61.0 ($\mathit{C}(CH_3)_2$), 72.8 ($\mathit{C}CH_3$), 93.4 (CH), 125.6, 127.2, 127.7, 128.4, 129.9, 137.2, 143.1 (C^{Ar}), 169.4, 170.4 (2 × CO) ppm. – MS (CI, isobutane): m/z (%) = 370.1 (23) $[M+H]^+$, 310.0 (100). – HRMS (CI, isobutane): m/z = 370.1477 (calcd. 370.1477 for $C_{21}H_{24}NO_3S$, $[M+H]^+$).

(4R,5R*)-3-Benzoyl-2,2,5-trimethyl-5-phenyl-1,3-thiazolidin-4-yl formate (**3b**)*

Following the GP, dihydrothiazole **1c** (2.05 g, 9.98 mmol), benzoyl chloride (1.55 g, 10.76 mmol) and sodium formate (2.72 g, 40.00 mmol) were used. A mixture of both racemic diastereomers was obtained as the crude product (2.13 g, 5.99 mmol, 60 %, *dr* = 61:39). For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 4 : 1, R_f = 0.37) to give the major racemic diastereomer as a colorless solid. M. p. 146 – 148 °C. – IR (ATR): ν = 2978, 2937, 1720, 1657, 1584, 1449, 1067, 700 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.45, 1.86 (2s, 6H, $C(CH_3)_2$), 2.10 (s, 3H, CCH_3), 7.14 (s, 1H, CH), 6.90 – 7.80 (m, 5H, CH^{Ar}), 7.96 (s, 1H, CHO) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 26.4, 29.9, 31.1 (3 × CH_3), 61.4 ($\mathit{C}(CH_3)_2$), 72.8 ($\mathit{C}CH_3$), 94.01 (CH), 125.6, 127.2, 127.7, 128.4, 128.5, 128.6, 129.1, 129.7, 129.8, 133.5, 137.2, 143.2 (C^{Ar}), 165.1 (CO), 170.5 (CHO) ppm. – MS (CI, isobutane): m/z (%) = 356.1 (100) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 356.1295 (calcd. 356.1294 for $C_{20}H_{22}NO_3S$, $[M+H]^+$).

(4R,5R*)-3-Acetyl-2,2,5-trimethyl-5-phenyl-1,3-thiazolidin-4-yl benzoate (**3c**)*

Following the GP, dihydrothiazole **1c** (2.05 g, 9.98 mmol), acetyl chloride (0.86 g, 10.96 mmol) and sodium benzoate (5.76 g, 39.97 mmol) were used. A mixture of both racemic diastereomers was obtained as the crude product (3.10 g, 8.39 mmol, 84 %, *dr* = 76:24). For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 4 : 1, R_f = 0.34) to give the major racemic diastereomer as a colorless oil. – IR (ATR): ν = 3063, 2980, 2931, 1745, 1659, 1344, 1211, 705 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.56, 1.72 ($C(CH_3)_2$), 1.98 (CCH_3), 2.13 ($COCH_3$), 6.98 (s, 1H, CH), 7.08 – 7.69 (m, 10H, CH^{Ar}) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 25.0, 26.6, 30.1, 30.4 (4 × CH_3), 60.8 ($\mathit{C}(CH_3)_2$), 73.3 ($\mathit{C}CH_3$), 92.5 (CH), 126.6, 127.6, 128.4, 128.5, 128.6, 128.7, 128.9, 129.3, 130.0, 130.1, 133.8, 143.5 (C^{Ar}), 166.0, 169.3 (2 × CO) ppm. – MS (CI, isobutane): m/z (%) = 370.1 (23) $[M+H]^+$, 248.1 (100). – HRMS (CI, isobutane): m/z = 370.1477 (calcd. 370.1477 for $C_{21}H_{24}NO_3S$, $[M+H]^+$).

(4R,5R*)-3-Acetyl-2,2,5-trimethyl-5-phenyl-1,3-thiazolidin-4-yl formate (**3d**)*

Following the GP, dihydrothiazole **1c** (4.10 g, 19.97 mmol), acetyl chloride (1.71 g, 21.79 mmol) and sodium formate (5.44 g, 79.99 mmol) were used. A mixture of both racemic diastereomers was obtained as the crude product (3.63 g, 12.37 mmol, 62 %, *dr* = 85:15). For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 4 : 1, R_f = 0.42) to give the major racemic diastereomer as a colorless solid. M. p. 116 – 118 °C. – IR (ATR): ν = 2979, 2933, 1715, 1664, 1496, 1444, 1088, 797 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.54, 1.64 (2s, 6H, $C(CH_3)_2$), 1.85 (s, 3H, CCH_3), 2.09 (s, 3H, $COCH_3$), 7.39 (s, 1H, CH), 7.25 – 7.72 (m, 5H, CH^{Ar}), 8.33 (s, 1H, CHO) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 24.8, 26.7, 29.9, 31.7 (4 × CH_3), 60.0 ($\mathit{C}(CH_3)_2$), 73.4 ($\mathit{C}CH_3$), 91.2 (CH), 126.4, 126.5, 127.5, 128.3, 128.5, 143.1 (C^{Ar}), 160.4 (CO), 168.8 (CHO) ppm. – MS (CI, isobutane): m/z (%) = 294.1 (100) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 294.1164 (calcd. 294.1164 for $C_{15}H_{20}NO_3S$, $[M+H]^+$).

(2R,4R*)-3-Benzoyl-2-tert-butyl-5,5-dimethyl-1,3-thiazolidin-4-yl acetate (**4a**)*

Following the GP, dihydrothiazole **1d** (3.42 g, 19.96 mmol), benzoyl chloride (3.09 g, 21.98 mmol) and sodium acetate (6.56 g, 79.97 mmol) were used. A mixture of both racemic diastereomers was obtained as the crude product (3.69 g, 11.00 mmol, 55 %, *dr* = 71:29). For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 4 : 1, R_f = 0.44) to give the major racemic diastereomer as a colorless solid. M. p. 77 – 80 °C. – IR (ATR): ν = 2961, 2870, 1748, 1669, 1603, 1341, 1219, 699 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.01 (s, 9H, $C(CH_3)_3$), 1.12, 1.20 (2s, 6H, $C(CH_3)_2$), 2.10 (s, 3H, $COCH_3$), 5.84 (s, 1H, $C\mathit{H}C(CH_3)_3$), 6.06 (s, 1H, NCH), 7.19 – 7.41 (m, 5H, CH^{Ar}) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 20.8 ($COCH_3$), 22.0, 29.0 ($C(\mathit{C}H_3)_2$), 27.3 ($C(\mathit{C}H_3)_3$), 37.5 ($\mathit{C}(CH_3)_3$), 54.9 ($\mathit{C}(CH_3)_2$), 71.2 ($\mathit{C}HC(CH_3)_3$), 92.3 (NCH), 127.5, 128.4,

128.5, 128.6, 131.5, 135.9 (C^{Ar}), 168.9, 173.5 (2 × CO) ppm. – MS (CI, isobutane): m/z (%) = 336.2 (20) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 336.1634 (calcd. 336.1633 for $C_{18}H_{26}NO_3S$, $[M+H]^+$).

(2R,4R*)-3-Benzoyl-2-tert-butyl-5,5-dimethyl-1,3-thiazolidin-4-yl formate (**4b**)*

Following the GP, dihydrothiazole **1d** (3.42 g, 19.96 mmol), benzoyl chloride (3.09 g, 21.98 mmol) and sodium formate (5.44 g, 79.99 mmol) were used. A mixture of both racemic diastereomers was obtained as the crude product (5.01 g, 15.59 mmol, 78 %, *dr* = 65:35). For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 7 : 3, R_f = 0.64) to give the major racemic diastereomer as a colorless solid. M. p. 83 °C. – IR (ATR): ν = 2964, 2872, 1742, 1680, 1436, 1280, 1177 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.17 (s, 9H, $C(CH_3)_3$), 1.22, 1.35 (2s, 6H, $C(CH_3)_2$), 5.97 (s, 1H, $CHC(CH_3)_3$), 6.44 (s, 1H, NCH), 7.32 – 8.12 (m, 5H, CH^{Ar}), 8.13 (s, 1H, CHO) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.1, 29.0 ($C(CH_3)_2$), 27.5 ($C(CH_3)_3$), 37.6 ($C(CH_3)_3$), 55.1 ($C(CH_3)_2$), 71.5 ($CHC(CH_3)_3$), 93.2 (NCH), 127.8, 128.6, 129.9, 131.7, 133.6, 135.8 (C^{Ar}), 164.9 (CO), 174.0 (CHO) ppm. – MS (CI, isobutane): m/z (%) = 322.1 (100) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 322.1475 (calcd. 322.1477 for $C_{17}H_{24}NO_3S$, $[M+H]^+$).

(2R,4R*)-3-Acetyl-2-tert-butyl-5,5-dimethyl-1,3-thiazolidin-4-yl benzoate (**4c**)*

Following the GP, dihydrothiazole **1d** (1.71 g, 9.98 mmol), acetyl chloride (0.86 g, 10.96 mmol) and sodium benzoate (5.76 g, 39.97 mmol) were used. A mixture of both racemic diastereomers was obtained as the crude product (2.68 g, 7.99 mmol, 80 %, *dr* = 92:8). For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 7 : 3, R_f = 0.56) to give the major racemic diastereomer as a colorless solid. M. p. 109 – 111 °C. – IR (ATR): ν = 3053, 2971, 2934, 1722, 1673, 1317, 1248, 709 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.97 (s, 9H, $C(CH_3)_3$), 1.38, 1.40 (2s, 6H, $C(CH_3)_2$), 2.44 ($COCH_3$), 5.70 (s, 1H, $CHC(CH_3)_3$), 6.61 (s, 1H, NCH), 7.40 – 8.11 (m, 5H, CH^{Ar}) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.3, 29.7 ($C(CH_3)_2$), 24.0 ($COCH_3$), 27.6 ($C(CH_3)_3$), 37.5 ($C(CH_3)_3$), 53.9 ($C(CH_3)_2$), 72.1 ($CHC(CH_3)_3$), 91.0 (NCH), 128.6, 128.7, 129.0, 129.9, 133.6 (C^{Ar}), 165.6, 172.3 (2 × CO) ppm. – MS (CI, isobutane): m/z (%) = 336.1 (100) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 336.1635 (calcd. 336.1633 for $C_{18}H_{26}NO_3S$, $[M+H]^+$).

(2R,4R*)-3-Acetyl-2-tert-butyl-5,5-dimethyl-1,3-thiazolidin-4-yl formate (**4d**)*

Following the GP, dihydrothiazole **1d** (3.42 g, 19.96 mmol), acetyl chloride (1.71 g, 21.79 mmol) and sodium formate (5.44 g, 79.99 mmol) were used. A mixture of both racemic diastereomers was obtained as the crude product (3.98 g, 15.35 mmol, 77 %, *dr* = 90:10). For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 7 : 3, R_f = 0.36) to give the major racemic diastereomer as a colorless solid. M. p. 65 °C. – IR (ATR): ν = 2974, 2871, 1720, 1675, 1437, 1282, 1137 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.94 (s, 9H, $C(CH_3)_3$), 1.32, 1.35 (2s, 6H, $C(CH_3)_2$), 2.34 (s, 3H, $COCH_3$), 5.63 (s, 1H, $CHC(CH_3)_3$), 6.41 (s, 1H, NCH), 8.17 (s, 1H, CHO) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.2, 29.7 ($C(CH_3)_2$), 23.8 ($COCH_3$), 27.5 ($C(CH_3)_3$), 37.5 ($C(CH_3)_3$), 53.4 ($C(CH_3)_2$), 72.0 ($CHC(CH_3)_3$), 89.9 (NCH), 160.0 (CO), 171.8 (CHO) ppm. – MS (CI, isobutane): m/z (%) = 260.1 (100) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 260.1320 (calcd. 260.1320 for $C_{12}H_{22}NO_3S$, $[M+H]^+$).

(2R,4R*)-3-Acetyl-2-tert-butyl-5,5-dimethyl-1,3-thiazolidin-4-yl acetate (**4e**)*

Following the GP, dihydrothiazole **1d** (1.71 g, 9.98 mmol), acetyl chloride (0.86 g, 10.96 mmol) and sodium acetate (3.28 g, 39.99 mmol) were used. A pure mixture of both racemic diastereomers was obtained as the crude product (3.93 g, 14.37 mmol, 72 %, *dr* > 95:5). For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 4 : 1, R_f = 0.31) to give the major racemic diastereomer as a colorless solid. M. p. 79–80 °C. – IR (ATR): ν = 2976, 2871, 1732, 1680, 1370, 1220 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 0.95 (s, 9H, $C(CH_3)_3$), 1.31, 1.33 (2s, 6H, $C(CH_3)_2$), 2.13 (s, 3H, $COCH_3$), 2.33 (s, 3H, $OCOCH_3$), 5.64 ($CHC(CH_3)_3$), 6.32 (NCH) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 20.9 ($OCOCH_3$), 22.0, 22.4 ($C(CH_3)_2$), 23.0 ($COCH_3$), 26.5 ($C(CH_3)_3$), 37.3 ($C(CH_3)_3$), 52.0 ($C(CH_3)_2$), 71.8 ($CHC(CH_3)_3$), 90.2 (NCH), 170.2, 172.0 (2 × CO) ppm. – MS (CI, isobutane): m/z (%) = 274.1 (100) $[M+H]^+$. – HRMS (CI, isobutane): m/z = 274.1476 (calcd. 274.1477 for $C_{13}H_{24}NO_3S$, $[M+H]^+$).

(2R,4R*)-2-tert-Butyl-5,5-dimethyl-3-[(2E)-3-phenylprop-2-enoyl]-1,3-thiazolidin-4-yl acetate (**4f**)*

Following the GP, dihydrothiazole **1d** (3.42 g, 19.96 mmol), cinnamoyl chloride (3.66 g, 21.79 mmol) and sodium acetate (6.56 g, 79.97 mmol) were used. A pure mixture of both racemic diastereomers was obtained as the crude product (6.02 g, 16.65 mmol, 83 %, *dr* = 74:26).

For analysis, the racemic diastereomers were purified by column chromatography on silica gel (solvent: *n*-hexane-ethyl acetate, 7 : 3, $R_f = 0.72$) to give the major racemic diastereomer as a colorless solid. M. p. 139–141 °C. – IR (ATR): ν = 2929, 2867, 1737, 1667, 1625, 1366, 1223, 1020, 976 cm^{-1}. – ^{1}H NMR (500.1 MHz, $CDCl_3$): $\delta = 0.99$ (s, 9H, $C(CH_3)_3$), 1.28, 1.34 (2s, 6H, $C(CH_3)_2$), 2.19 (s, 3H, $COCH_3$), 5.85 (s, 1H, $CHC(CH_3)_3$), 6.50 (d, $^3J = 16.0$ Hz, 1H, C*H*=CHPh), 6.63 (s, 1H, NCH), 7.35 – 7.69 (m, 5H, CH^{Ar}), 7.86 (d, $^3J = 16.0$ Hz, 1H, CH=C*H*Ph) ppm. – ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.0 ($COCH_3$), 22.0, 26.8 ($C(CH_3)_2$), 27.3 ($C(CH_3)_3$), 37.4 ($C(CH_3)_3$), 53.8 ($C(CH_3)_2$), 71.7 ($CHC(CH_3)_3$), 90.3 (NCH), 119.5 (*C*H=CHPh), 128.1, 128.2, 128.3, 129.0, 134.7, 134.7 (C^{Ar}), 144.1 (CH=*C*HPh), 168.0, 170.4 (2 × CO) ppm. – MS (CI, isobutane): m/z (%) = 362.2 (20) $[M+H]^+$, 302.2 (100). – HRMS (CI, isobutane): m/z = 362.1790 (calcd. 362.1790 for $C_{20}H_{28}NO_3S$, $[M+H]^+$).

X-Ray structure determinations

Intensity data for the single-crystal structure determinations were collected on a Stoe IPDS diffractometer at 153(2) K with MoK_α radiation (graphite monochromator, $\lambda = 0.71073$ Å). The structures were solved by Direct Methods and refined by full-matrix least-squares methods with SHELXS-97 [42] and SHELXL-97 [43], respectively. Non-hydrogen atoms were refined with anisotropic displacement parameters. All H atoms were placed in calculated positions and refined using the riding model. Crystallographic data can be found in Table 5.

CCDC883999 (**3a**) and 884000 (**4e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 5. Crystal structure data for compounds (R^*,R^*)-**3a** and (R^*,R^*)-**4e**.

	(R^*,R^*)-**3a**	(R^*,R^*)-**4e**
Formula	$C_{21}H_{23}NO_3S$	$C_{13}H_{23}NO_3S$
M_r	369.46	273.38
Crystal size, mm^3	0.80 × 0.55 × 0.46	0.90 × 0.62 × 0.52
Crystal system	triclinic	monoclinic
Space group	$P\bar{1}$	$I2/a$
a, Å	9.4139(9)	11.2959(7)
b, Å	10.1088(11)	10.5879(5)
c, Å	11.2714(12)	24.8405(18)
α, deg	108.424(12)	90
β, deg	95.482(12)	91.669(8)
γ, deg	107.578(12)	90
V, Å^3	948.25(17)	2969.7(3)
Z	2	8
D_{calcd}, g cm^{-3}	1.29	1.22
μ (MoK_α), cm^{-1}	1.9	2.2
F(000), e	392	1184
hkl range	±11, ±12, −14 → 13	±13, ±13, ±30
$((\sin\theta)/\lambda)_{max}$, Å^{-1}	1.271	1.259
Refl. measured/ unique/R_{int}	11 946/3553/ 0.0536	15 730/2941/ 0.0496
Param. refined	304	232
$R(F)/wR(F^2)$[a,b] (all data)	0.0547/0.0680	0.0403/0.0713
GoF (F^2)[c]	0.829	0.890
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	0.274/−0.211	0.260/−0.151

[a] $R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; [b] $wR(F^2) = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w = [\sigma^2(F_o^2) + (AP)^2 + BP]^{-1}$, where $P = (\mathrm{Max}(F_o^2,0) + 2F_c^2)/3$; [c] GoF = $[\Sigma w(F_o^2 - F_c^2)^2/(n_{obs} - n_{param})]^{1/2}$.

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