EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201094

An Asymmetric Organocatalytic Approach to Michael Reactions of Thiazolones and Nitroalkenes: Preparation of Compounds with Anti-Cancer Potency

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Keywords: Organocatalysis / Asymmetric catalysis / Michael addition / Biological activity / Medicinal chemistry / Antitumor agents

We present a highly efficient strategy for obtaining a series of chiral 2,4-disubstituted thiazolone derivatives with excellent diastereo- and enantioselectivities through the creation of carbon- and nitrogen-substituted quaternary carbon stereocenters. With the chiral tertiary amine-thiourea catalyst developed by our group, the reactions could be performed smoothly at 1 mol-% catalyst loadings without any additive. Preliminary biological evaluation demonstrated that these analogues could inhibit cell proliferation in vitro significantly.

Introduction

During the past decades, increasing comprehension of the mechanism of drug interaction on a molecular level has led to greatly increased awareness of the importance of chirality as a key to the efficacy of many medicinal products.[1] It is now well known that generally only one stereoisomer of a pharmaceutical is required for efficacy and that other stereoisomers are either inactive or exhibit considerably reduced activities. Accordingly, many new drugs in clinical use and under development consist of single optically active isomers to avoid the possibility of side effects due to undesirable stereoisomers.[2]

Thiazole heterocyclic systems are ubiquitous in numerous natural molecules that have been isolated and shown to exhibit significant pharmaceutical activities.[3] The thiazolidinone moiety, for instance, is known to be associated with antibiotic, immunosuppressive, and antitumor properties and so has come to occupy a prominent position in the drug discovery process.[4] Moreover, a number of naturally occurring molecules containing the aminothiazole ring structure have been applied in several drugs marketed for the treatment of HIV infection, hypertension, and inflammation (Figure 1).[5] The established utility of these five-membered heterocyclic structures in medicinal chemistry has drawn special attention in the construction of their derivatives. Although a number of synthetic strategies for the synthesis of these thiazole derivatives have been developed, especially for 2,4-disubstituted thiazole analogues, almost all of these studies have until now been focused on the racemic forms.[6] Exploitation of new organocatalyst methodologies for the preparation of thiazole derivatives with drug activities in enantiopure forms would therefore be an important advancement for expanding their pharmaceutical usage.

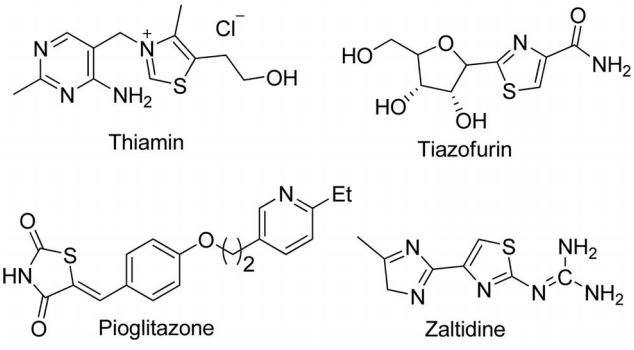

Figure 1. Examples of pharmaceuticals containing thiazole ring moieties.

In 2010, some asymmetric examples of the use of 2-(benzyloxy)thiazol-5(4*H*)-ones in catalytic synthesis were reported by Ooi's group, who used a C_1-symmetric chiral ammonium betaine as catalyst and obtained high stereoselectivities.[7] Subsequently, an organocatalytic approach for the preparation of chiral 2-(ethylthio)thiazolone adducts,

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201094.

several of which were found to show potential anticancer activities, was developed by our group.[8] Consequently, we believed that optically active addition products of other electrophilic reagents with thiazolones might also be attractive. Because of the easy transformations that allow further reactions based on the nitro functionality, we demonstrate here a new organocatalytic approach using nitroalkenes as electrophilic reagents to react with racemic 2,4-disubstituted thiazolones, a previously little-studied field. These reactions led efficiently, in one-step manner, to a series of chiral 2,4-disubstituted thiazolone derivatives (CDTDs) each containing two new chiral centers.

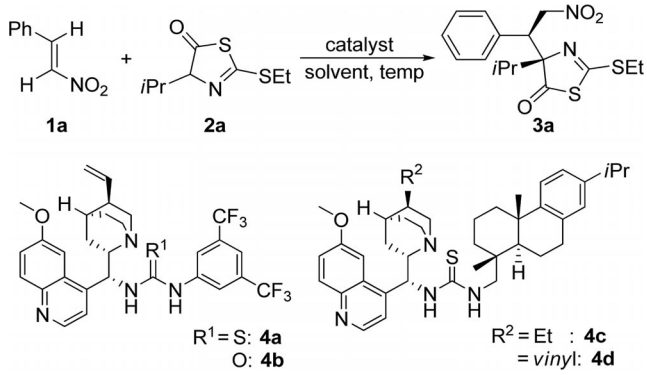
Results and Discussion

To achieve the desired enantioselective conjugate addition, reactions between 2,4-disubstituted thiazolones and nitroalkenes in the presence of various organocatalysts and solvents were investigated (Table 1). We hoped to take the advantage of what we had learned from the reactions between *N*-tosyl aldimines and 2-(ethylthio)thiazolones; initial results were not encouraging, however, because the quinidine catalyst gave the adduct **3a** in racemic form (Entry 2), whereas use of quinine and TMSQ as catalysts separately gave 33% and 13% *ee* values (Entries 1 and 3). During the course of optimization, it was found that the bifunctional thiourea-tertiary amine **4a**, which performed deficiently in the Mannich addition, could afford the adduct **3a** with a good diastereomeric ratio and a 73% *ee* (Entry 4). Use of urea catalyst **4b**, with the same configuration, resulted in dramatic decreases in stereoselectivities, probably as the result of decreased hydrogen bonding (Entry 5). Finally, we used thiourea catalysts **4c** and **4d**, with bulky groups, which were developed by our group.[9] It was found that both performed well, with **4d** giving the best result (Entries 6 and 7).

Subsequently the effects of different solvents were investigated; MTBE proved to be optimal (Entries 8–10). With the goal of improving the enantioselectivity further, we conducted a cursory examination of the influence of the reaction temperature. When the reaction temperature was lowered to 0 °C, a higher *ee* value of 94% with a maintained diastereomeric ratio was achieved (Entry 11). Further cooling resulted in longer reaction time and decreased stereoselectivities. Under –80 °C, the level of conversion of **1a** was still under 70% after 36 h (Entry 13).

With the optimized condition established, we explored the scope of the enantioselective additions between 2,4-disubstituted thiazolones and nitroalkenes in the presence of **4d** (10 mol-%) at 0 °C, as shown in Table 2. Of the reactions with the 2,4-disubstituted thiazolone **2a** as nucleophile, the majority proceeded smoothly to furnish the corresponding masked CDTDs in moderate to good yields and with excellent diastereo- and enantioselectivities. The aromatic nitroalkenes tolerated substitutions at any position in their aromatic rings, and both electron-donating and electron-withdrawing functionalities were compatible (Entries 1–18). The

Table 1. Initial reaction optimization.[a]



Entry	Catalyst (10 mol-%)	*T* [°C]	Solvent	*t* [h]	*dr* (% *ee*)
1	quinine	r.t.	Et_2O	6	5:1 (33)
2	quinidine	r.t.	Et_2O	6	4:1 (0)
3	TMSQ[b]	r.t.	Et_2O	6	4:1 (13)
4	**4a**	r.t.	Et_2O	6	5:1 (73)
5	**4b**	r.t.	Et_2O	8	4:1 (–11)
6	**4c**	r.t.	Et_2O	5	3:1 (81)
7	**4d**	r.t.	Et_2O	5	5:1 (89)
8[c]	**4d**	r.t.	solvent	5	6:1 (86)
9	**4d**	r.t.	anisole	8	4:1 (85)
10	**4d**	r.t.	MTBE	5	5:1 (92)
11	**4d**	0	MTBE	6	5:1 (94)
12	**4d**	–40	MTBE	18	4:1 (92)
13[d]	**4d**	–80	MTBE	36	<4:1 (84)

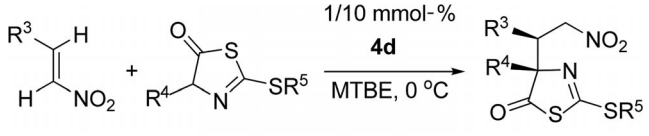
[a] Unless indicated otherwise, all reactions were performed with **1a** (0.10 mmol) and **2a** (0.15 mmol) in solvent (1.0 mL) for 5–8 h, and full conversion was observed in all cases. *Dr* values were determined by ^1H NMR measurements before purification; *ee* values were determined by chiral HPLC on a Chiralpak OD column. [b] TMSQ is quinine with a TMS protecting group. [c] The solvent was cyclohexyl methyl ether. [d] The level of conversion of the reactant was under 70% after 36 h.

substrate **1l** gave the best result: the corresponding adduct **3l** was obtained in good yield with a 10:1 *dr* and a 96% *ee* value (Entry 12). A somewhat longer reaction time was required for a 2,5-dimethoxy-substituted nitroalkene (Entry 19), due to its inherently lower reactivity toward nucleophiles, but it still gave excellent results.

The additions of more sterically hindered 1-naphthyl- and 2-naphthyl-derived nitroalkenes proceeded equally well, with excellent enantioselectivities and good diastereoselectivities (Entries 20 and 21). Heteroaromatic nitroolefins were also viable substrates (Entries 22 and 23). With alkyl nitroalkenes the reactivity was less, and so we utilized alkenyl-substituted nitroalkene **1x** as the synthetic equivalent of alkyl nitroalkenes in Entry 24. The reaction was performed for 12 h and selectively gave adduct **3x** with moderate results.

Furthermore, several different substituted 2,4-disubstituted thiazolones were evaluated and also found to be good substrates for this method (Entries 26–28). A high enantioselectivity (92%) with a moderate diastereomeric ratio (4:1) was observed when the 2,4-disubstituted thiazolone had a benzyl substituent at the R^5 position. A longer reaction

Table 2. Scope of the reaction.[a]



1a–y **2a–d** **3a–z'**

Entry	R^3, R^4, R^5	**3**, *t* [h], % yield[b]	*dr* (% *ee*)
1[c]	Ph, *i*Pr, Et	**3a**, 6, 81 (80)	5:1 (94) (5:1, 92)
2	2-F-Ph, *i*Pr, Et	**3b**, 8, 87	9:1 (95)
3[c]	4-F-Ph, *i*Pr, Et	**3c**, 8, 74 (63)	8:1 (93) (8:1, 91)
4[c]	2-Cl-Ph, *i*Pr, Et	**3d**, 6, 83 (69)	9:1 (96) (9:1, 95)
5[c]	3-Cl-Ph, *i*Pr, Et	**3e**, 6, 83 (71)	8:1 (94) (8:1, 91)
6[c]	4-Cl-Ph, *i*Pr, Et	**3f**, 10, 82 (67)	8:1 (94) (7:1, 93)
7[c]	2-Br-Ph, *i*Pr, Et	**3g**, 6, 84 (75)	7:1 (94) (7:1, 92)
8	3-Br-Ph, *i*Pr, Et	**3h**, 8, 70	7:1 (94)
9[c]	4-Br-Ph, *i*Pr, Et	**3i**, 8, 87	6:1 (94)
10	2-Me-Ph, *i*Pr, Et	**3j**, 6, 65	7:1 (90)
11	4-Me-Ph, *i*Pr, Et	**3k**, 6, 83	8:1 (92)
12[c]	2-NO_2-Ph, *i*Pr, Et	**3l**, 6, 84 (76)	10:1 (96) (9:1, 95)
13	3-NO_2-Ph, *i*Pr, Et	**3m**, 8, 79	6:1 (93)
14	4-NO_2-Ph, *i*Pr, Et	**3n**, 8, 73	5:1 (92)
15	3-MeO-Ph, *i*Pr, Et	**3o**, 8, 64	9:1 (96)
16[c]	4-MeO-Ph, *i*Pr, Et	**3p**, 8, 75 (71)	8:1 (91) (9:1, 90)
17	4-CN-Ph, *i*Pr, Et	**3q**, 6, 71	7:1 (94)
18	3,4- $(Me)_2$-Ph, *i*Pr, Et	**3r**, 6, 83	9:1 (92)
19	2,5- $(MeO)_2$-Ph, *i*Pr, Et	**3s**, 24, 71	9:1 (96)
20[c]	1-naphthyl, *i*Pr, Et	**3t**, 12, 64 (60)	3:1 (92) (3:1, 92)
21	2-naphthyl, *i*Pr, Et	**3u**, 36, 82	6:1 (83)
22[d]	2-furyl, *i*Pr, Et	**3v**, 12, 93	4:1 (88/83)
23	2-thienyl, *i*Pr, Et	**3w**, 36, 80	5:1 (87)
24[d]	(*E*)-Ph-CH=CH-, *i*Pr, Et	**3x**, 12, 66	1:4 (97/70)
25[e]	cyclohexyl, *i*Pr, Et	–, 48, –	nd (nd)
26	2-NO_2-Ph, *t*Bu, Et	**3y**, 8, 62	3:1 (80)
27	4-CN-Ph, *t*Bu, Et	**3z**, 18, 68	9:1 (84)
28	4-CN-Ph, *i*Pr, Bn	**3z′**, 12, 71	4:1 (92)

[a] For experimental details, see the Supporting Information. [b] Isolated yields. [c] The reactions were also performed with 0.001 mmol of **4d**; results are shown in brackets. [d] The yields of both diastereoisomers. [e] Under the optimized conditions, the substrate **1y** showed no reactivity toward 2-(ethylthio)thiazolone **2a**.

time was required for substrate **2c**, presumably due to steric hindrance of the tertiary butyl group at the R^4 position (Entry 27).

The relative and absolute configurations of the products were determined with the aid of an X-ray crystal structure analysis of **3i** (Figure 2).[10]

In view of the case in which we had obtained a series of CDTDs, we decided to evaluate the compounds' anticancer activities. Using a colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, we investigated cytotoxic activities against five human cancer cell lines (T-24, PC-3, MDA-MB-231, HeLa, and HepG-2); a summary of the IC_{50} values is shown in Table 3. In sharp contrast to compounds derived from *N*-tosyl aldimines, the analogues derived from nitroalkenes exhibited significant increases in cytotoxic activities. In experiments in which a 1-naphthyl substituent was present at the R^3 position of the compound, exciting IC_{50} values were found with all the cancer cells, in particular with 3.52 μM in the HeLa cell. The IC_{50} values also showed that the replacement of the aliphatic substituent at the R^4 position had little influence on the cytotoxic activities. However, the activities of the compounds decreased when a benzyl substituent was present at the R^5 position. We can conclude that the nitro functionality is an important candidate for the cytotoxic activities of CDTDs and that the modification of substituents R^3 and R^5 can further improve their activities in the presence of the nitro group.

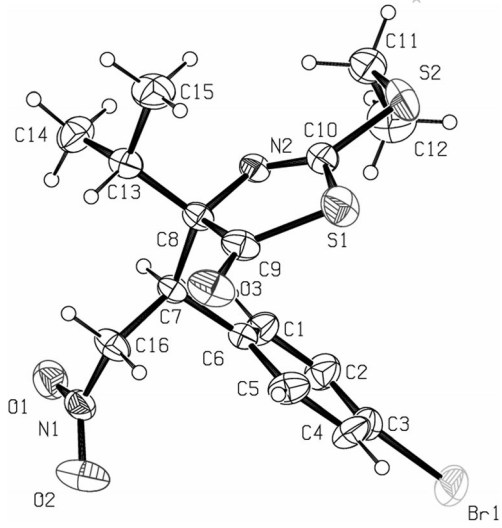


Figure 2. X-ray structure of the adduct **3i**.

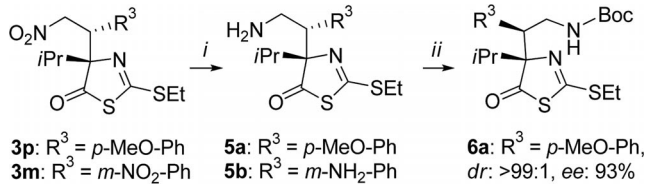
Conversion of the nitro groups in adducts **3** into primary amine groups might improve the compounds' water-solubilities and bioavailabilities, due to the hydrogen-bonding interaction between the primary amine group and the oxo group, so we prepared chiral derivatives **5a** and **5b** (Scheme 1), containing primary amine groups, in 78% and 82% yields, respectively. Compound **5a** could also be easily converted into compound **6a** with retention of diastereoselectivity and enantioselectivity. Unfortunately, the cytotoxic activities exhibited loss on PC-3 cells, the inhibition of growth decreased from 56% (with **3p**) to 23% (with **5a**) and 61% (with **3m**) to 22% (with **5b**) separately when the chiral adducts **5** were used. It was concluded that the nitro groups played a positive role in the cytotoxic activities of these analogues.

Because we had demonstrated that the CDTDs displayed significant cytotoxic activities, we decided to explore the potential of this reaction for practical application further. Firstly, we tested the additions between 2,4-disubstituted thiazolones and nitroalkenes at 1 mol-% catalyst loading to evaluate the potential of the catalyst **4d**. To our delight, the majority of the adducts were obtained with maintained diastereoselectivities and only slightly decreased enantioselectivities, albeit with generally prolonged reaction times and slightly reduced yields (Table 2, data in brackets in Entries 1, 3–7, 12, 16, and 20). A reaction was then carried out on a gram scale, and an adduct was obtained with a perfect enantioselectivity (>99% *ee* value) and only slightly decreased diastereoselectivity (Scheme 2).

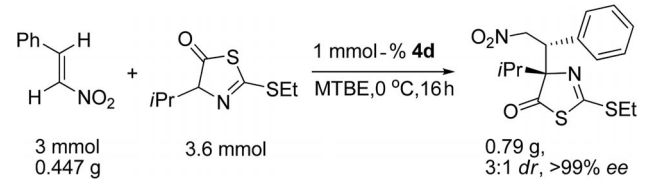
Table 3. IC_{50} values of CDTDs on the growth of human cancer cell lines.[a]

Entry	Adduct	MDA-MB-231	T-24	HeLa	HepG-2	PC-3
1	**3a**	23.03				
2	**3b**	30.58	20.94	19.06	28.26	35.19
3	**3c**	16.39	19.48	14.74	19.78	26.73
4	**3d**	26.72	17.46	17.25	29.84	20.01
5	**3e**	31.29	17.21	13.89	18.16	13.75
6	**3f**	13.98	17.66	8.29	22.17	16.01
7	**3g**	19.75	12.17	12.24	15.72	17.83
8	**3h**	26.43	16.43	13.73	18.94	11.31
9	**3i**	20.64	12.28	32.15	17.73	11.63
10	**3j**	17.24	22.95	20.82	19.87	17.42
11	**3k**	27.17	21.81	15.55	21.76	17.23
12	**3l**	15.17	9.48	10.62	15.18	12.72
13	**3m**	20.36	13.83	10.02	20.04	14.11
14	**3n**	10.23	15.09	15.83	15.69	11.6
15	**3o**	16.71	15.42	16.4	22.54	19.21
16	**3p**	18.13	17.28	11.04	20.53	13.56
17	**3q**	13.11	11.23	10.38	18.78	12.73
18	**3r**	15.4	23.72	14.13	19.89	22.34
19	**3t**	6.14	4.17	3.52	8.05	7.11
20	**3w**	37.48	24.91	22.84	35.15	39.69
21	**3y**	13.46	8.72	6.67	15.577	11.79
22	**3z**	15.34	13.26	13.07	18.51	13.14
23	**3z′**	29.97	17.86	14.64	20.5	16.5

[a] Values were means of three experiments, each done in duplicate. IC_{50} values are expressed in μM. MDA, T-24, HeLa, HepG-2, and PC-3 cells were seeded at a density of 5000 cells mL^{-1} in 96-well plates. Compounds were added 24 h after seeding. After 2 d in culture, the MTT stock solution (5 mg mL^{-1} in PBS) was added to each well and the mixture was incubated at 37 °C for 4 h. The medium was removed carefully, and dimethyl sulfoxide was added to each well to dissolve formazan. The absorbance of each well at 490 nm was measured with a Bio-Rad Model 680 microplate reader.



Scheme 1. Transformations of the products. Reagents and conditions: *i*) $SnCl_2$, concd. HCl, EtOH, room temp.; *ii*) $(Boc)_2O$, Et_3N, THF, room temp.



Scheme 2. Preparative-scale experiment.

Conclusions

In summary, we report the synthesis of optically active 2,4-disubstituted thiazolone derivatives with high levels of enantio- and diastereoselectivity (up to 96% *ee* and 10:1 *dr*) through asymmetric organocatalysis in Michael reactions. The additions of thiazolones to nitroalkenes were catalyzed by the tertiary amine-thiourea catalyst developed by our group. Under mild conditions, the reactions could be performed efficiently with catalyst loadings as low as 1 mol-% without any additive. These new derivatives were found to show high inhibitory effects on the viabilities of five types of cancer cells in vitro. This preliminary study might provide a basic strategy for the further development of new chiral heterocycle compounds with anti-cancer potency.

Experimental Section

General Procedure for the Additions between 2,4-Disubstituted Thiazolones and Nitroalkenes: A nitroalkene **1** (0.10 mmol) was added at 0 °C to a mixture of a 2,4-disubstituted thiazolone **2** (0.15 mmol) and catalyst **4d** (0.01 mmol/0.001 mmol) in MTBE (1.0 mL). After the reaction was complete (as determined by TLC), the reaction mixture was concentrated, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate 9:1) to afford the product **3**.

Cytotoxicity Assay: The modified colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma–Aldrich) assay is a widely used "in vitro' assay for quantifying cell proliferation and viability that determines reduction in cell viability on the basis of reduction of the tetrazolium salt by actively growing cells to produce a blue formazan product. The MTT test was performed as described previously, with some modifications. Briefly, cells (5000 cells per well) were cultured in 96-well plates (Costar) for 24 h. The old culture medium was replaced with fresh, and the cells were incubated with various concentrations of compounds for an additional 48 h. After this period of time, the MTT stock solution (5 mg mL^{-1} in PBS) was added to each well and incubation was carried out at 37 °C for 4 h. The medium was removed carefully and dimethyl sulfoxide was added to each well to dissolve formazan. The absorbance of each well at 490 nm was measured with a Bio-Rad Model 680 microplate reader. Experiments were performed in duplicate and repeated at least three times. The IC_{50} value was calculated from the semi-logarithmic dose–response curves.

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-2-nitro-1-phenylethyl]thiazol-5(4*H*)-one: Compound **3a** was isolated by column chromatography on silica gel as a single diastereoisomer in 81% yield (28.6 mg, diastereomeric ratio 5:1), or in 80% yield (28.2 mg, diastereomeric ratio 5:1) when 1 mol-% **4d** was used. White solid; m.p. 108–109 °C. $[a]_D^{20}$ = +23.3 (*c* = 2.49 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.31 (m, 2 H), 7.29 (dd, *J* = 6.5, 3.3 Hz, 3 H), 4.92 (dd, *J* = 12.8, 11.9 Hz, 1 H), 4.64 (dd, *J* = 13.0, 3.7 Hz, 1 H), 4.18 (dd, *J* = 11.8, 3.7 Hz, 1 H), 3.34–3.06 (m, 2 H), 2.22–2.05 (m, 1 H), 1.42 (t, *J* = 7.4 Hz, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7 (s), 162.1 (s), 134.4 (s), 129.4 (s), 128.3 (s), 92.9 (s), 75.6 (s), 48.4 (s), 34.3 (s), 25.4 (s), 17.1 (s), 16.3 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1718, 1559, 1456, 1378, 1265, 973, 849, 753, 702 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{20}N_2O_3S_2 + H]^+$ 353.0988; found 353.0981. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 7.5, t_{minor} = 9.7, 94% *ee*).

(*S*)-2-(Ethylthio)-4-[(*S*)-1-(2-fluorophenyl)-2-nitroethyl]-4-isopropylthiazol-5(4*H*)-one: Compound **3b** was isolated by column chromatography on silica gel as a single diastereoisomer in 87% yield (32.3 mg, diastereomeric ratio 9:1). White solid; m.p. 104–105

°C. $[a]_D^{20}$ = +38.8 (*c* = 2.06 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 (t, *J* = 7.3 Hz, 1 H), 7.32–7.21 (m, 1 H), 7.14–6.95 (m, 2 H), 4.95 (t, *J* = 12.9 Hz, 1 H), 4.72 (dd, *J* = 13.6, 3.6 Hz, 2 H), 3.26 (tt, *J* = 14.7, 7.4 Hz, 1 H), 3.17–3.01 (m, 1 H), 2.28–2.06 (m, 1 H), 1.39 (t, *J* = 7.4 Hz, 3 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.9 (s), 162.8 (s), 162.0 (s), 159.5 (s), 130.1 (d, *J* = 8.6 Hz), 124.2 (d, *J* = 3.5 Hz), 121.8 (d, *J* = 13.5 Hz), 115.9 (s), 115.6 (s), 92.9 (s), 74.6 (s), 34.5 (s), 25.3 (s), 17.3 (s), 16.6 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1719, 1559, 1493, 1377, 1233, 1108, 973, 759 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}FN_2O_3S_2 + H]^+$ 371.0894; found 371.0887. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 5.8, t_{minor} = 6.9, 95% *ee*).

(*S*)-2-(Ethylthio)-4-[(*S*)-1-(4-fluorophenyl)-2-nitroethyl]-4-isopropylthiazol-5(4*H*)-one: Compound **3c** was isolated by column chromatography on silica gel as a single diastereoisomer in 74% yield (27.4 mg, diastereomeric ratio 8:1), or in 63% yield (23.3 mg, diastereomeric ratio 8:1) when 1 mol-% **4d** was used. White solid; m.p. 93–94 °C. $[a]_D^{20}$ = +17.7 (*c* = 1.07 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.28 (m, 2 H), 6.98 (t, *J* = 8.7 Hz, 2 H), 4.97–4.79 (m, 1 H), 4.64 (dd, *J* = 13.0, 3.8 Hz, 1 H), 4.17 (dd, *J* = 11.9, 3.8 Hz, 1 H), 3.36–3.05 (m, 2 H), 2.11 (hept, *J* = 6.7 Hz, 1 H), 1.42 (t, *J* = 7.4 Hz, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.6 (s), 164.2 (s), 162.5 (s), 160.9 (s), 131.0 (d, *J* = 8.3 Hz), 129.9 (d, *J* = 3.4 Hz), 115.5 (s), 115.2 (s), 92.9 (s), 75.6 (s), 47.6 (s), 34.3 (s), 25.4 (s), 17.1 (s), 16.3 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2973, 1722, 1559, 1511, 1378, 1231, 974, 823, 660 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}FN_2O_3S_2 + H]^+$ 371.0894; found 371.0889. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 5.6, t_{minor} = 7.0, 92% *ee*).

(*S*)-4-[(*S*)-1-(2-Chlorophenyl)-2-nitroethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **3d** was isolated by column chromatography on silica gel as a single diastereoisomer in 83% yield (32.1 mg, diastereomeric ratio 9:1), or in 69% yield (26.7 mg, diastereomeric ratio 9:1) when 1 mol-% **4d** was used. White solid; m.p. 109–110 °C. $[a]_D^{20}$ = +2.79 (*c* = 1.43 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.40 (m, 1 H), 7.35 (dt, *J* = 7.3, 3.7 Hz, 1 H), 7.24–7.16 (m, 2 H), 5.09 (dd, *J* = 11.3, 3.7 Hz, 1 H), 4.94 (t, *J* = 12.2 Hz, 1 H), 4.79 (dd, *J* = 13.0, 3.7 Hz, 1 H), 3.41–3.17 (m, 1 H), 3.05 (dq, *J* = 14.7, 7.4 Hz, 1 H), 2.23 (dt, *J* = 13.8, 6.9 Hz, 1 H), 1.36 (t, *J* = 7.4 Hz, 3 H), 1.26 (t, *J* = 6.4 Hz, 4 H), 0.88 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.8 (s), 161.4 (s), 136.1 (s), 132.6 (s), 130.0 (s), 129.4 (s), 128.1 (s), 126.9 (s), 93.4 (s), 75.1 (s), 60.4 (s), 43.1 (s), 34.7 (s), 25.2 (s), 17.4 (s), 16.9 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2971, 1715, 1558, 1471, 1376, 1207, 1038, 971, 754 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}ClN_2O_3S_2 + H]^+$ 387.0698; found 387.0606. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 6.1, t_{minor} = 6.9, 96% *ee*).

(*S*)-4-[(*S*)-1-(3-Chlorophenyl)-2-nitroethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **3e** was isolated by column chromatography on silica gel as a single diastereoisomer in 83% yield (32.1 mg, diastereomeric ratio 8:1), or in 71% yield (27.4 mg, diastereomeric ratio 8:1) when 1 mol-% **4d** was used. White solid; m.p. 90–91 °C. $[a]_D^{20}$ = +4.2 (*c* = 1.9 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39 (s, 1 H), 7.31–7.17 (m, 3 H), 4.87 (dd, *J* = 13.1, 11.8 Hz, 1 H), 4.64 (dd, *J* = 13.2, 3.7 Hz, 1 H), 4.16 (dd, *J* = 11.8, 3.7 Hz, 1 H), 3.36–3.10 (m, 2 H), 2.21–2.02 (m, 1 H), 1.44 (t, *J* = 7.4 Hz, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.4 (s), 162.7 (s), 136.3 (s), 134.1 (s), 129.9 (s), 129.6 (s), 128.6 (s), 127.2 (s), 92.6 (s), 75.2 (s), 47.9 (s), 34.3 (s), 25.4 (s), 17.1 (s), 16.3 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1717, 1559, 1472, 1377, 1082, 974, 697 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}ClN_2O_3S_2 + H]^+$ 387.0598; found 387.0593. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 5.6, t_{minor} = 6.5, 94% *ee*).

(*S*)-4-[(*S*)-1-(4-Chlorophenyl)-2-nitroethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **3f** was isolated by column chromatography on silica gel as a single diastereoisomer in 82% yield (31.7 mg, diastereomeric ratio 8:1), or in 67% yield (25.9 mg, diastereomeric ratio 7:1) when 1 mol-% **4d** was used. White solid; m.p. 61–62 °C. $[a]_D^{20}$ = +16.8 (*c* = 2.08 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 5 H), 4.86 (dd, *J* = 13.0, 11.9 Hz, 1 H), 4.62 (dd, *J* = 13.1, 3.8 Hz, 1 H), 4.16 (dd, *J* = 11.8, 3.8 Hz, 1 H), 3.33–3.04 (m, 2 H), 2.09 (dq, *J* = 13.5, 6.8 Hz, 1 H), 1.42 (t, *J* = 7.4 Hz, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.4 (s), 162.6 (s), 134.4 (s), 132.7 (s), 130.7 (s), 128.6 (s), 92.7 (s), 75.4 (s), 47.7 (s), 34.3 (s), 25.4 (s), 17.0 (s), 16.2 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2971, 1718, 1558, 1492, 1377, 973, 753 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}ClN_2O_3S_2 + H]^+$ 387.0598; found 387.0576. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 6.1, t_{minor} = 7.6, 93% *ee*).

(*S*)-4-[(*S*)-1-(2-Bromophenyl)-2-nitroethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **3g** was isolated by column chromatography on silica gel as a single diastereoisomer in 84% yield (36.2 mg, diastereomeric ratio 7:1), or in 75% yield (32.3 mg, diastereomeric ratio 7:1) when 1 mol-% **4d** was used. White solid; m.p. 100–101 °C. $[a]_D^{20}$ = –3.8 (*c* = 1.84 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.40 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.30–7.21 (m, 1 H), 7.12 (td, *J* = 7.7, 1.7 Hz, 1 H), 5.10 (dd, *J* = 11.3, 3.7 Hz, 1 H), 5.02–4.90 (m, 1 H), 4.81 (dd, *J* = 13.0, 3.7 Hz, 1 H), 3.35 (tt, *J* = 14.7, 7.3 Hz, 1 H), 3.12–2.97 (m, 1 H), 2.25 (hept, *J* = 6.6 Hz, 1 H), 1.36 (t, *J* = 7.4 Hz, 3 H), 1.31 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.0 (s), 161.2 (s), 134.2 (s), 133.3 (s), 129.7 (s), 128.0 (s), 127.4 (d, *J* = 14.0 Hz), 93.3 (s), 75.0 (s), 45.9 (s), 34.7 (s), 25.2 (s), 17.5 (s), 17.0 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2971, 1715, 1559, 1467, 1377, 972, 754 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}BrN_2O_3S_2 + H]^+$ 431.0093; found 431.0080. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 6.5, t_{minor} = 7.4, 94% *ee*).

(*S*)-4-[(*S*)-1-(3-Bromophenyl)-2-nitroethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **3h** was isolated by column chromatography on silica gel as a single diastereoisomer in 70% yield (30.2 mg, diastereomeric ratio 7:1). White solid; m.p. 105–107 °C. $[a]_D^{20}$ = –3.8 (*c* = 0.8 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 7.43 (ddd, *J* = 7.9, 1.9, 1.1 Hz, 1 H), 7.34–7.22 (m, 1 H), 7.16 (t, *J* = 7.8 Hz, 1 H), 4.87 (dd, *J* = 13.2, 11.8 Hz, 1 H), 4.64 (dd, *J* = 13.2, 3.7 Hz, 1 H), 4.15 (dd, *J* = 11.8, 3.7 Hz, 1 H), 3.35–3.09 (m, 2 H), 2.12 (hept, *J* = 6.6 Hz, 1 H), 1.45 (t, *J* = 7.4 Hz, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.3 (s), 162.7 (s), 136.5 (s), 132.9 (s), 131.5 (s), 129.9 (s), 127.5 (s), 122.3 (s), 92.6 (s), 75.2 (s), 47.8 (s), 34.2 (s), 25.5 (s), 17.1 (s), 16.3 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1716, 1559, 1471, 1377, 1201, 1072, 974, 785, 697 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}BrN_2O_3S_2 + H]^+$ 431.0093; found 431.0099. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 6.2, t_{minor} = 7.1, 94% *ee*).

(*S*)-4-[(*S*)-1-(4-Bromophenyl)-2-nitroethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **3i** was isolated by column

chromatography on silica gel as a single diastereoisomer in 87% yield (37.5 mg, diastereomeric ratio 6:1). White solid; m.p. 71–72 °C. $[a]_D^{20}$ = +8.97 (*c* = 3.23 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 (t, *J* = 5.4 Hz, 2 H), 7.30–7.19 (m, 2 H), 4.85 (dd, *J* = 13.0, 11.9 Hz, 1 H), 4.62 (dd, *J* = 13.1, 3.8 Hz, 1 H), 4.15 (dd, *J* = 11.8, 3.8 Hz, 1 H), 3.33–3.06 (m, 2 H), 2.10 (hept, *J* = 6.7 Hz, 1 H), 1.42 (t, *J* = 7.4 Hz, 3 H), 1.08 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.3 (s), 162.6 (s), 133.3 (s), 131.5 (s), 131.0 (s), 122.5 (s), 92.6 (s), 75.4 (s), 47.8 (s), 34.3 (s), 25.4 (s), 17.0 (s), 16.2 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1717, 1558, 1488, 1377, 1073, 974, 908, 737, 650 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}BrN_2O_3S_2 + H]^+$ 431.0093; found 431.0084. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 6.5, t_{minor} = 8.1, 94% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-2-nitro-1-*o*-tolylethyl]thiazol-5(4*H*)-one: Compound **3j** was isolated by column chromatography on silica gel as a single diastereoisomer in 65% yield (23.9 mg, diastereomeric ratio 7:1). White solid; m.p. 87–88 °C. $[a]_D^{20}$ = +27.38 (*c* = 0.84 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.22 (m, 2 H), 7.15–7.04 (m, 3 H), 5.05 (dd, *J* = 13.3, 11.7 Hz, 1 H), 4.81 (dd, *J* = 13.3, 3.7 Hz, 1 H), 4.69 (dd, *J* = 11.7, 3.7 Hz, 1 H), 3.15 (dq, *J* = 13.2, 7.4 Hz, 1 H), 2.95 (dq, *J* = 13.2, 7.4 Hz, 1 H), 2.42 (s, 3 H), 2.27 (hept, *J* = 6.6 Hz, 1 H), 1.34–1.27 (m, 6 H), 0.85 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.4 (s), 161.2 (s), 138.2 (s), 132.9 (s), 130.6 (s), 128.0 (s), 126.1 (s), 126.0 (s), 93.6 (s), 75.2 (s), 42.4 (s), 34.6 (s), 25.0 (s), 20.1 (s), 17.5 (s), 17.1 (s), 14.5 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2967, 1708, 1553, 1441, 1377, 1266, 969, 738 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{22}N_2O_3S_2 + H]^+$ 367.1145; found 367.1149. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{minor} = 6.1, t_{major} = 7.2, 90% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-2-nitro-1-*p*-tolylethyl]thiazol-5(4*H*)-one: Compound **3k** was isolated by column chromatography on silica gel as a single diastereoisomer in 83% yield (30.5 mg, diastereomeric ratio 8:1). White solid; m.p. 101–102 °C. $[a]_D^{20}$ = +12.8 (*c* = 1.88 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.18 (m, 3 H), 7.08 (d, *J* = 7.9 Hz, 2 H), 4.86 (dd, *J* = 12.7, 11.9 Hz, 1 H), 4.61 (dd, *J* = 12.8, 3.8 Hz, 1 H), 4.13 (dd, *J* = 11.8, 3.8 Hz, 1 H), 3.35–3.05 (m, 2 H), 2.31 (s, 3 H), 2.12 (hept, *J* = 6.6 Hz, 1 H), 1.42 (t, *J* = 7.4 Hz, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.6 (s), 161.9 (s), 138.0 (s), 131.0 (s), 129.2 (s), 129.0 (s), 93.0 (s), 75.8 (s), 48.1 (s), 34.2 (s), 25.3 (s), 21.1 (s), 17.0 (s), 16.2 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2971, 1720, 1458, 1558, 1377, 973 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{22}N_2O_3S_2 + H]^+$ 367.1145; found 367.1150. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 5.1, t_{minor} = 5.7, 92% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-2-nitro-1-(2-nitrophenyl)ethyl]-thiazol-5(4*H*)-one: Compound **3l** was isolated by column chromatography on silica gel as a single diastereoisomer in 84% yield (33.4 mg, diastereomeric ratio 10:1), or in 76% yield (30.2 mg, diastereomeric ratio 9:1) when 1 mol-% **4d** was used. White solid; m.p. 99–100 °C. $[a]_D^{20}$ = –161.4 (*c* = 1.4 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.62–7.37 (m, 3 H), 5.60 (dd, *J* = 11.6, 3.9 Hz, 1 H), 5.26 (dd, *J* = 13.4, 11.7 Hz, 1 H), 4.97 (dd, *J* = 13.5, 3.9 Hz, 1 H), 3.33 (dq, *J* = 13.4, 7.4 Hz, 1 H), 2.90 (dq, *J* = 13.3, 7.4 Hz, 1 H), 2.25 (hept, *J* = 6.7 Hz, 1 H), 1.38–1.26 (m, 6 H), 0.82 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.7 (s), 163.1 (s), 151.1 (s), 132.6 (s), 129.1 (s), 128.6 (s), 128.0 (s), 125.2 (s), 93.3 (s), 73.3 (s), 40.0 (s), 34.5 (s), 25.1 (s), 17.4 (s), 17.2 (s), 14.1 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1716, 1558, 1446, 1354, 973, 852, 664 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}N_3O_5S_2 + H]^+$ 398.0839; found 398.0844. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 9.9, t_{minor} = 11.8, 96% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-2-nitro-1-(3-nitrophenyl)ethyl]-thiazol-5(4*H*)-one: Compound **3m** was isolated by column chromatography on silica gel as a single diastereoisomer in 79% yield (31.4 mg, diastereomeric ratio 6:1). White solid; m.p. 86–87 °C. $[a]_D^{20}$ = –20.1 (*c* = 1.94 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.41 (s, 1 H), 8.18 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1 H), 7.73–7.62 (m, 1 H), 7.50 (t, *J* = 8.0 Hz, 1 H), 4.91 (dd, *J* = 13.2, 12.0 Hz, 1 H), 4.69 (dd, *J* = 13.4, 3.7 Hz, 1 H), 4.31 (dd, *J* = 11.9, 3.7 Hz, 1 H), 3.36 (dq, *J* = 13.3, 7.4 Hz, 1 H), 3.27–3.11 (m, 1 H), 2.08 (hept, *J* = 6.8 Hz, 1 H), 1.46 (t, *J* = 7.4 Hz, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.8 (s), 163.4 (s), 147.9 (s), 136.5 (s), 135.1 (s), 129.4 (s), 124.8 (s), 123.4 (s), 92.4 (s), 75.1 (s), 47.7 (s), 34.3 (s), 25.6 (s), 17.0 (s), 16.1 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2973, 1717, 1559, 1462, 1350, 1095, 975, 736, 692 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}N_3O_5S_2 + H]^+$ 398.0839; found 398.0835. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 9.4, t_{minor} = 11.7, 93% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-2-nitro-1-(4-nitrophenyl)ethyl]-thiazol-5(4*H*)-one: Compound **3n** was isolated by column chromatography on silica gel as a single diastereoisomer in 73% yield (29.0 mg, diastereomeric ratio 5:1). White solid; m.p. 91–92 °C. $[a]_D^{20}$ = +22.7 (*c* = 2.11 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.9 Hz, 2 H), 7.62–7.48 (m, 2 H), 4.94 (dd, *J* = 13.4, 11.9 Hz, 1 H), 4.70 (dd, *J* = 13.4, 3.7 Hz, 1 H), 4.32 (dd, *J* = 11.9, 3.7 Hz, 1 H), 3.28 (dq, *J* = 13.3, 7.4 Hz, 1 H), 3.14 (dq, *J* = 13.2, 7.4 Hz, 1 H), 2.11 (dt, *J* = 6.6 Hz, 1 H), 1.43 (t, *J* = 7.4 Hz, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.0 (s), 163.3 (s), 147.8 (s), 141.8 (s), 130.3 (s), 123.4 (s), 92.5 (s), 74.9 (s), 47.9 (s), 34.4 (s), 25.5 (s), 17.1 (s), 16.3 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2973, 1716, 1559, 1348, 974, 861, 699 cm^{-1}. HRMS (ESI): calcd. for $[C_{16}H_{19}N_3O_5S_2 + H]^+$ 398.0839; found 398.0836. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 12.4, t_{minor} = 17.5, 92% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-1-(3-methoxyphenyl)-2-nitroethyl]thiazol-5(4*H*)-one: Compound **3o** was isolated by column chromatography on silica gel as a single diastereoisomer in 64% yield (24.5 mg, diastereomeric ratio 9:1). White solid; m.p. 52–53 °C. $[a]_D^{20}$ = +7.7 (*c* = 1.16 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 8.2 Hz, 1 H), 6.97–6.89 (m, 2 H), 6.82 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1 H), 4.86 (dd, *J* = 12.9, 11.7 Hz, 1 H), 4.61 (dd, *J* = 12.9, 3.7 Hz, 1 H), 4.15 (dd, *J* = 11.7, 3.7 Hz, 1 H), 3.78 (s, 3 H), 3.36–3.07 (m, 2 H), 2.15 (hept, *J* = 6.7 Hz, 1 H), 1.42 (t, *J* = 7.4 Hz, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5 (s), 162.1 (s), 159.3 (s), 135.8 (s), 129.3 (s), 121.7 (s), 115.3 (s), 113.7 (s), 92.9 (s), 75.8 (s), 55.1 (s), 48.4 (s), 34.3 (s), 25.4 (s), 17.1 (s), 16.3 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2970, 1718, 1558, 1461, 1378, 1262, 1047, 974, 701 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{22}N_2O_4S_2 + H]^+$ 383.1094; found 383.1089. HPLC (Chiralpak AS-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 8.8, t_{minor} = 15.5, 96% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-1-(4-methoxyphenyl)-2-nitroethyl]thiazol-5(4*H*)-one: Compound **3p** was isolated by column chromatography on silica gel as a single diastereoisomer in 75% yield (28.7 mg, diastereomeric ratio 8:1), or in 71% yield (27.2 mg,

diastereomeric ratio 9:1) when 1 mol-% **4d** was used. White solid; m.p. 62–63 °C. $[\alpha]_D^{20}$ = +10.5 (*c* = 1.53 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 8.6, 3.1 Hz, 1 H), 6.81 (d, *J* = 8.9 Hz, 1 H), 4.93–4.80 (m, 1 H), 4.60 (dd, *J* = 12.8, 3.8 Hz, 1 H), 4.12 (dd, *J* = 11.9, 3.8 Hz, 1 H), 3.78 (s, 1 H), 3.36–3.07 (m, 1 H), 2.11 (hept, *J* = 6.6 Hz, 1 H), 1.43 (t, *J* = 7.4 Hz, 1 H), 1.08 (d, *J* = 6.9 Hz, 1 H), 0.91 (d, *J* = 6.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7 (s), 161.9 (s), 159.3 (s), 130.4 (s), 125.9 (s), 113.7 (s), 93.1 (s), 75.8 (s), 55.1 (s), 47.7 (s), 34.2 (s), 25.3 (s), 17.0 (s), 16.2 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2970, 1720, 1558, 1513, 1461, 1378, 1252, 1181, 1035, 973 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{22}N_2O_4S_2 + H]^+$ 383.1094; found 383.1088. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 6.3, t_{minor} = 6.9, 91% *ee*).

4-{(*S*)-1-[(*S*)-2-(Ethylthio)-4-isopropyl-5-oxo-4,5-dihydrothiazol-4-yl]-2-nitroethyl}benzonitrile: Compound **3q** was isolated by column chromatography on silica gel as a single diastereoisomer in 71% yield (26.8 mg, diastereomeric ratio 7:1). Colorless oil. $[\alpha]_D^{20}$ = +31 (*c* = 1.29 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.5 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 4.92 (dd, *J* = 13.3, 11.9 Hz, 1 H), 4.68 (dd, *J* = 13.4, 3.7 Hz, 1 H), 4.25 (dd, *J* = 11.9, 3.7 Hz, 1 H), 3.37–3.02 (m, 2 H), 2.10 (hept, *J* = 6.6 Hz, 1 H), 1.42 (t, *J* = 7.4 Hz, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.1 (s), 163.2 (s), 139.8 (s), 132.0 (s), 130.1 (s), 118.2 (s), 112.4 (s), 92.5 (s), 74.8 (s), 48.1 (s), 34.4 (s), 25.4 (s), 17.1 (s), 16.3 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 2231, 1717, 1558, 1457, 1377, 974, 863 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{19}N_3O_3S_2 + H]^+$ 378.0941; found 378.0943. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 12.3, t_{minor} = 16.9, 94% *ee*).

(*S*)-4-[(*S*)-1-(3,4-Dimethylphenyl)-2-nitroethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **3r** was isolated by column chromatography on silica gel as a single diastereoisomer in 83% yield (31.6 mg, diastereomeric ratio 9:1). White solid; m.p. 99–100 °C. $[\alpha]_D^{20}$ = +4.7 (*c* = 1.9 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (s, 1 H), 7.11–6.98 (m, 3 H), 4.86 (dd, *J* = 12.8, 11.8 Hz, 1 H), 4.60 (dd, *J* = 12.8, 3.7 Hz, 1 H), 4.10 (dd, *J* = 11.7, 3.7 Hz, 1 H), 3.33–3.09 (m, 2 H), 2.21 (s, 6 H), 2.18–2.06 (m, 1 H), 1.43 (t, *J* = 7.4 Hz, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7 (s), 161.7 (s), 136.6 (s), 136.3 (s), 131.4 (s), 130.9 (s), 129.5 (s), 126.4 (s), 93.0 (s), 75.8 (s), 48.0 (s), 34.2 (s), 25.3 (s), 19.8 (s), 19.4 (s), 17.0 (s), 16.3 (s), 14.8 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2971, 1720, 1558, 1454, 1377, 973 cm^{-1}. HRMS (ESI): calcd. for $[C_{18}H_{24}N_2O_3S_2 + H]^+$ 381.1301; found 381.1309. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{minor} = 7.3, t_{major} = 8.0, 92% *ee*).

(*S*)-4-[(*S*)-1-(2,5-Dimethoxyphenyl)-2-nitroethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **3s** was isolated by column chromatography on silica gel as a single diastereoisomer in 71% yield (29.3 mg, diastereomeric ratio 9:1). Yellow oil. $[\alpha]_D^{20}$ = –45.9 (*c* = 2.42 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 13.0 Hz, 1 H), 6.80 (dd, *J* = 7.2, 3.2 Hz, 2 H), 5.08–4.75 (m, 1 H), 4.75–4.34 (m, 2 H), 3.75 (s, 6 H), 3.15 (s, 2 H), 2.18 (d, *J* = 6.6 Hz, 1 H), 1.38 (s, 3 H), 1.12–0.92 (m, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.9 (s), 161.4 (s), 153.2 (s), 152.0 (s), 124.5 (s), 113.9 (s), 112.1 (s), 55.5 (s), 34.7 (s), 29.7 (s), 25.2 (s), 17.2 (s), 15.6 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2969, 1722, 1558, 1501, 1462, 1378, 1224, 1050, 973, 808, 744 cm^{-1}. HRMS (ESI): calcd. for $[C_{18}H_{24}N_2O_5S_2 + H]^+$ 413.1199; found 413.1189. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{minor} = 6.6, t_{major} = 7.2, 96% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-1-(naphthalen-1-yl)-2-nitroethyl]thiazol-5(4*H*)-one: Compound **3t** was isolated by column chromatography on silica gel as a single diastereoisomer in 64% yield (25.8 mg, diastereomeric ratio 3:1), or in 60% yield (24.2 mg, diastereomeric ratio 3:1) when 1 mol-% **4d** was used. White solid; m.p. 75–76 °C. $[\alpha]_D^{20}$ = –34.4 (*c* = 1.57 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.6 Hz, 1 H), 7.84–7.73 (m, 2 H), 7.58 (dt, *J* = 3.0, 1.4 Hz, 1 H), 7.56–7.50 (m, 1 H), 7.46 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1 H), 7.42–7.34 (m, 1 H), 5.37 (dd, *J* = 11.4, 3.8 Hz, 1 H), 5.22 (dd, *J* = 13.0, 11.4 Hz, 1 H), 4.95 (dd, *J* = 13.1, 3.7 Hz, 1 H), 2.81 (dq, *J* = 13.2, 7.4 Hz, 1 H), 2.50 (dq, *J* = 13.2, 7.4 Hz, 1 H), 2.32 (hept, *J* = 6.7 Hz, 1 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.04 (t, *J* = 7.4 Hz, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.3 (s), 161.3 (s), 133.8 (s), 132.8 (s), 130.7 (s), 129.0 (s), 128.7 (s), 126.1 (s), 125.5 (s), 124.8 (s), 124.8 (s), 123.7 (s), 93.8 (s), 75.4 (s), 41.0 (s), 34.6 (s), 24.8 (s), 17.6 (s), 17.1 (s), 14.1 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2970, 1715, 1558, 1460, 1377, 972, 777 cm^{-1}. HRMS (ESI): calcd. for $[C_{20}H_{22}N_2O_3S_2 + H]^+$ 403.1145; found 403.1135. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 7.2, t_{minor} = 8.3, 92% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-1-(naphthalen-2-yl)-2-nitroethyl]thiazol-5(4*H*)-one: Compound **3u** was isolated by column chromatography on silica gel as a single diastereoisomer in 82% yield (33.0 mg, diastereomeric ratio 6:1). White solid; m.p. 110–111 °C. $[\alpha]_D^{20}$ = –9.7 (*c* = 3.1 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 11.4, 6.4 Hz, 4 H), 7.55–7.41 (m, 3 H), 5.10–4.93 (m, 1 H), 4.70 (dd, *J* = 13.0, 3.7 Hz, 1 H), 4.36 (dd, *J* = 11.7, 3.7 Hz, 1 H), 3.35–3.10 (m, 2 H), 2.25–2.07 (m, 1 H), 1.43 (t, *J* = 7.4 Hz, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.6 (s), 162.2 (s), 133.0 (s), 132.9 (s), 131.7 (s), 128.9 (s), 128.0 (s), 128.0 (s), 127.6 (s), 126.7 (s), 126.4 (s), 126.3 (s), 93.0 (s), 75.8 (s), 48.5 (s), 34.4 (s), 25.4 (s), 17.1 (s), 16.2 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2971, 1718, 1558, 1461, 1377, 1267, 973, 818, 749 cm^{-1}. HRMS (ESI): calcd. for $[C_{20}H_{22}N_2O_3S_2 + H]^+$ 403.1145; found 403.1152. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 80:20, flow rate 1.0 mL min^{-1}, retention time: t_{minor} = 7.2, t_{major} = 10.5, 83% *ee*).

(*S*)-2-(Ethylthio)-4-[(*S*)-1-(furan-2-yl)-2-nitroethyl]-4-isopropylthiazol-5(4*H*)-one: Compound **3v** was isolated by column chromatography on silica gel. The two diastereoisomers were obtained in a yield of 93% (31.9 mg, diastereomeric ratio 4:1). Colorless oil. $[\alpha]_D^{20}$ = –5.24 (*c* = 2.67 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (ddd, *J* = 2.4, 1.8, 0.9 Hz, 1 H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1 H), 6.21 (d, *J* = 3.1 Hz, 1 H), 4.98 (dd, *J* = 13.2, 11.7 Hz, 1 H), 4.67 (dd, *J* = 13.2, 3.5 Hz, 1 H), 4.33 (dd, *J* = 11.7, 3.5 Hz, 1 H), 3.29–3.07 (m, 2 H), 2.17 (dq, *J* = 13.4, 6.7 Hz, 1 H), 1.41 (t, *J* = 7.3 Hz, 3 H), 1.17 (d, *J* = 6.8 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.2 (s), 162.5 (s), 148.2 (s), 142.7 (s), 110.5 (s), 109.9 (s), 92.1 (s), 73.5 (s), 42.2 (s), 34.1 (s), 25.4 (s), 17.1 (s), 16.6 (s), 14.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1722, 1560, 1462, 1377, 1267, 1149, 974, 742 cm^{-1}. HRMS (ESI): calcd. for $[C_{14}H_{18}N_2O_4S_2 + H]^+$ 343.0781; found 343.0774. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 98:2, flow rate 1.0 mL min^{-1}, retention time: t_{1major} = 7.2, t_{1minor} = 9.6, t_{2major} = 7.5, t_{2minor} = 8.7, 88%/83% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*)-2-nitro-1-(thiophen-2-yl)ethyl]-thiazol-5(4*H*)-one: Compound **3w** was isolated by column chromatography on silica gel as a single diastereoisomer in 80% yield (28.7 mg, diastereomeric ratio 5:1). White solid; m.p. 40–41

°C. $[\alpha]_D^{20}$ = –19.6 (*c* = 1.8 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 5.2, 0.8 Hz, 1 H), 7.01 (dd, *J* = 3.5, 1.0 Hz, 1 H), 6.93 (dd, *J* = 5.1, 3.5 Hz, 1 H), 4.67 (dd, *J* = 12.3, 11.4 Hz, 1 H), 4.60–4.44 (m, 2 H), 3.38 (dq, *J* = 13.3, 7.4 Hz, 1 H), 3.23 (dq, *J* = 13.3, 7.4 Hz, 1 H), 2.19 (hept, *J* = 6.9 Hz, 1 H), 1.48 (t, *J* = 7.4 Hz, 3 H), 1.00 (dd, *J* = 6.8, 2.2 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.3 (s), 163.0 (s), 136.4 (s), 128.5 (s), 126.6 (s), 126.4 (s), 92.5 (s), 44.3 (s), 34.4 (s), 25.7 (s), 16.7 (s), 15.8 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1720, 1559, 1436, 1377, 973, 705 cm^{-1}. HRMS (ESI): calcd. for $[C_{14}H_{18}N_2O_3S_3 + H]^+$ 359.0552; found 359.0543. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 6.4, t_{minor} = 8.5, 87% *ee*).

(*S*)-2-(Ethylthio)-4-isopropyl-4-[(*S*,*E*)-1-nitro-4-phenylbut-3-en-2-yl]-thiazol-5(4*H*)-one: Compound **3x** was isolated by column chromatography on silica gel. The two diastereoisomers were obtained in a yield of 66% (25.0 mg, diastereomeric ratio 1:4). White solid; m.p. 30–31 °C. $[\alpha]_D^{20}$ = –30.3 (*c* = 2.01 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 4 H), 7.29–7.24 (m, 1 H), 6.56 (d, *J* = 15.8 Hz, 1 H), 6.13–5.99 (m, 1 H), 4.55–4.37 (m, 2 H), 3.81 3.67 (m, 1 H), 3.38–3.11 (m, 2 H), 2.33–2.17 (m, 1 H), 1.44 (dt, *J* = 10.0, 7.4 Hz, 3 H), 1.06 (dd, *J* = 6.8, 3.1 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, main): δ = 209.7 (s), 162.2 (s), 136.7 (s), 136.0 (s), 128.5 (s), 128.2 (s), 126.6 (s), 122.2 (s), 92.4 (s), 75.5 (s), 47.0 (s), 34.2 (s), 25.4 (s), 16.9 (s), 15.8 (s), 14.7 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 1721, 1558, 1450, 1378, 1333, 972, 749 cm^{-1}. HRMS (ESI): calcd. for $[C_{18}H_{22}N_2O_3S_2 + H]^+$ 379.1145; found 379.1149. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{1major} = 6.0, t_{1minor} = 22.4, t_{2minor} = 6.5, t_{2major} = 7.0, 97%/70% *ee*).

(*S*)-2-(Ethylthio)-4-isobutyl-4-[(*S*)-2-nitro-1-(2-nitrophenyl)ethyl]thiazol-5(4*H*)-one: Compound **3y** was isolated by column chromatography on silica gel as a single diastereoisomer in 62% yield (25.5 mg, diastereomeric ratio 3:1). White solid; m.p. 97–98 °C. $[\alpha]_D^{20}$ = –47.1 (*c* = 1.55 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 8.1, 1.3 Hz, 1 H), 7.67 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.59 (td, *J* = 7.7, 1.3 Hz, 1 H), 7.52–7.42 (m, 1 H), 5.14 (dd, *J* = 10.8, 4.4 Hz, 1 H), 4.89 (dd, *J* = 13.7, 10.8 Hz, 1 H), 4.78 (dd, *J* = 13.7, 4.5 Hz, 1 H), 3.28 (dq, *J* = 13.2, 7.4 Hz, 1 H), 3.12 (dq, *J* = 13.1, 7.4 Hz, 1 H), 1.88 (dd, *J* = 13.9, 6.5 Hz, 1 H), 1.76 (dd, *J* = 13.9, 5.5 Hz, 1 H), 1.69–1.52 (m, 1 H), 1.38 (t, *J* = 7.4 Hz, 3 H), 0.85 (dd, *J* = 6.6, 2.3 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.1 (s), 162.7 (s), 151.3 (s), 132.7 (s), 129.2 (s), 129.2 (s), 128.7 (s), 125.0 (s), 90.1 (s), 74.9 (s), 45.7 (s), 43.5 (s), 25.2 (s), 24.4 (s), 24.2 (s), 24.0 (s), 14.3 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2962, 1720, 1558, 1446, 1355, 971, 735 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{21}N_3O_5S_2 + H]^+$ 412.0995; found 412.1005. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{minor} = 7.5, t_{major} = 10.2, 80% *ee*).

4-{(*S*)-1-[(*R*)-4-*tert*-Butyl-2-(ethylthio)-5-oxo-4,5-dihydrothiazol-4-yl]-2-nitroethyl}benzonitrile: Compound **3z** was isolated by column chromatography on silica gel as a single diastereoisomer in 68% yield (26.7 mg, diastereomeric ratio 9:1). Colorless oil. $[\alpha]_D^{20}$ = –30.2 (*c* = 2.15 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.3 Hz, 2 H), 7.46 (d, *J* = 8.3 Hz, 2 H), 5.41 (dd, *J* = 13.8, 4.4 Hz, 1 H), 4.89 (dd, *J* = 13.8, 10.1 Hz, 1 H), 4.46 (dd, *J* = 10.1, 4.4 Hz, 1 H), 2.61 (dq, *J* = 11.7, 7.5 Hz, 1 H), 2.42 (dq, *J* = 11.7, 7.4 Hz, 1 H), 1.25 (t, *J* = 7.5 Hz, 3 H), 1.15 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7 (s), 174.5 (s), 138.7 (s), 131.9 (s), 130.4 (s), 118.0 (s), 113.0 (s), 91.6 (s), 75.9 (s), 52.9 (s), 36.0 (s), 27.3 (s), 24.2 (s), 13.6 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2971, 2231, 1705, 1558, 1438, 1373, 867, 735 cm^{-1}. HRMS (ESI): calcd. for $[C_{18}H_{21}N_3O_3S_2 + H]^+$ 392.1097; found 392.1086. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 12.9, t_{minor} = 10.7, 84% *ee*).

4-{(*S*)-1-[(*S*)-2-(Benzylthio)-4-isopropyl-5-oxo-4,5-dihydrothiazol-4-yl]-2-nitroethyl}benzonitrile: Compound **3z′** was isolated by column chromatography on silica gel as a single diastereoisomer in 71% yield (31.2 mg, diastereomeric ratio 4:1). White solid; m.p. 133–134 °C. $[\alpha]_D^{20}$ = +51.3 (*c* = 1.91 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.5 Hz, 2 H), 7.44–7.36 (m, 4 H), 7.36–7.28 (m, 1 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 4.79 (dd, *J* = 13.3, 11.9 Hz, 1 H), 4.60 (dd, *J* = 13.4, 3.8 Hz, 1 H), 4.47–4.31 (m, 2 H), 4.15 (dd, *J* = 11.9, 3.7 Hz, 1 H), 2.03 (dd, *J* = 13.5, 6.8 Hz, 1 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 0.83 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.7 (s), 162.4 (s), 139.5 (s), 135.9 (s), 131.9 (s), 130.1 (s), 128.7 (s), 128.7 (s), 127.9 (s), 118.3 (s), 112.3 (s), 92.6 (s), 74.5 (s), 48.0 (s), 35.0 (s), 34.2 (s), 17.0 (s), 16.2 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 2972, 2230, 1720, 1558, 1454, 1377, 977, 703 cm^{-1}. HRMS (ESI): calcd. for $[C_{22}H_{21}N_3O_3S_2 + H]^+$ 440.1097; found 440.1090. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, retention time: t_{minor} = 36.8, t_{major} = 41.1, 92% *ee*).

Transformation of Adduct 3 Into Compounds 5 and 6: Concd. aqueous HCl (0.2 mL) was added at 0 °C to a stirred solution of compound **3** (0.1 mmol) and $SnCl_2$ (0.8 mmol) in EtOH (1 mL). The reaction was stirred for 4 h at room temperature and monitored by TLC. After the reaction was complete, the mixture was concentrated under reduced pressure and diluted with CH_2Cl_2 (2 mL). The mixture was then made basic to pH 9 with ammonia and quenched with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were dried with Na_2SO_4 and purified by flash silica chromatography (DCM/MeOH 40:1, R_f = 0.4) to afford **5**.

$(Boc)_2O$ (0.12 mmol) was added at room temperature to a stirred solution of the major diastereoisomer of compound **5** (0.1 mmol) and EtN_3 (0.15 mmol) in THF (2 mL). The mixture was then stirred for 6 h at the same temperature. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (petroleum ether/ethyl acetate 9:1) to afford **6** (91% yield).

(*S*)-4-[(*S*)-2-Amino-1-(4-methoxyphenyl)ethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **5a** was isolated by column chromatography on silica gel as a single diastereoisomer in 78% yield (28.8 mg, diastereomeric ratio 9:1). Colorless oil. $[\alpha]_D^{20}$ = +6.6 (*c* = 0.75 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.3 Hz, 2 H), 6.94 (s, 1 H), 6.76 (d, *J* = 8.3 Hz, 2 H), 4.01 (d, *J* = 13.5 Hz, 1 H), 3.83 (dd, *J* = 13.4, 5.2 Hz, 2 H), 3.75 (s, 3 H), 3.24 (s, 1 H), 3.13–2.87 (m, 2 H), 1.20–1.03 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7 (s), 158.6 (s), 130.4 (s), 128.9 (s), 114.1 (s), 113.4 (s), 77.4 (s), 77.0 (s), 76.6 (s), 70.2 (s), 56.4 (s), 55.2 (s), 44.7 (s), 34.5 (s), 30.0 (s), 18.3 (s), 16.9 (s), 13.9 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3300, 2966, 1698, 1513, 1362, 1247, 1181, 1031, 833 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{24}N_2O_2S_2 + NH_4]^+$ 370.1617; found 370.1629.

(*S*)-4-[(*S*)-2-Amino-1-(3-aminophenyl)ethyl]-2-(ethylthio)-4-isopropylthiazol-5(4*H*)-one: Compound **5b** was isolated by column chromatography on silica gel as a single diastereoisomer in 82% yield (29.1 mg, diastereomeric ratio 10:1). Colorless oil. $[\alpha]_D^{20}$ = –78.0 (*c* = 0.5 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.02 (t, *J* = 7.8 Hz, 2 H), 6.69 (d, *J* = 7.7 Hz, 2 H), 6.60–6.48 (m, 1 H), 5.59 (s, 2 H), 3.99 (t, *J* = 7.7 Hz, 1 H), 3.91–3.71 (m, 2 H), 3.21 (s, 1 H), 3.13–2.90 (m, 2 H), 1.12 (m, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.8 (s), 166.1 (s), 145.8 (s), 139.7 (s), 128.9 (s), 119.8 (s), 116.3 (s), 114.2 (s), 77.4 (s), 77.0 (s), 76.6 (s), 70.1 (s), 55.9 (s),

45.2 (s), 34.5 (s), 30.0 (s), 18.3 (s), 17.0 (s), 14.0 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3310, 2926, 1698, 1612, 1498, 1364, 1015, 911, 732 cm^{-1}. HRMS (ESI): $[C_{16}H_{23}N_3OS_2 + NH_4]^+$ calcd. for 355.1621; found 355.1642.

***tert*-Butyl (*S*)-2-[(*S*)-2-(Ethylthio)-4-isopropyl-5-oxo-4,5-dihydrothiazol-4-yl]-2-(4-methoxyphenyl)ethylcarbamate:** Compound **6a** was isolated by column chromatography on silica gel as a single diastereoisomer in 91% yield (42.7 mg, diastereomeric ratio >99:1). Colorless oil. $[\alpha]_D^{20}$ = –1.1 (*c* = 1.8 in $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 2 H), 6.86 (s, 1 H), 6.79 (t, *J* = 5.9 Hz, 2 H), 3.98 (dt, *J* = 12.1, 7.6 Hz, 2 H), 3.83 (d, *J* = 5.4 Hz, 1 H), 3.77 (s, 3 H), 3.20 (s, 1 H), 3.01 (q, *J* = 7.3 Hz, 2 H), 1.56 (s, 9 H), 1.20–1.06 (m, 9 H), 0.91–0.81 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.9 (s), 166.5 (s), 158.7 (s), 150.8 (s), 130.4 (s), 113.4 (s), 86.2 (s), 77.4 (s), 77.0 (s), 76.6 (s), 68.7 (s), 55.2 (s), 54.6 (s), 44.4 (s), 34.5 (s), 30.0 (s), 27.5 (s), 18.2 (s), 16.9 (s), 14.0 (s) ppm. IR ($CDCl_3$): $\tilde{\nu}$ = 3291, 2974, 1789, 1732, 1514, 1368, 1251, 1151, 1026, 834, 733 cm^{-1}. HRMS (ESI): calcd. for $[C_{22}H_{32}N_2O_4S_2 + NH_4]^+$ 470.2142; found 470.2127. HPLC (Chiralpak OD-H column, *n*-hexane/*i*PrOH 95:5, flow rate 1.0 mL min^{-1}, retention time: t_{major} = 9.6, t_{minor} = 14.0, 93% *ee*).

Supporting Information (see footnote on the first page of this article): Detailed biological studies, copies of spectra of all products and X-ray information of compound **3i**.

Acknowledgments

We are grateful for grants from the National Natural Science Foundation of China (NSFC) (grant numbers 20932003 and 90813012) and the Key National S & T Major Project and Major New Drugs Development of China (grant number 2012ZX09504-001-003).

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[10] CCDC-843118 contains 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/daa_request/cif.

Received: August 13, 2012
Published Online: October 9, 2012

