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Diastereoselective and Catalytic α-Alkylation of Chiral *N*-Acyl Thiazolidinethiones with Stable Carbocationic Salts

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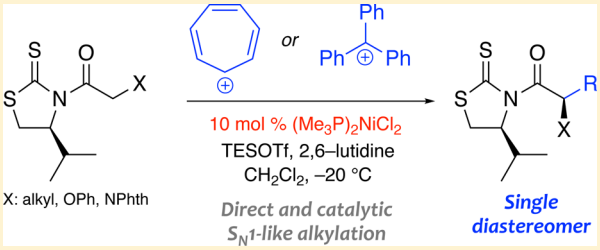
Supporting Information

ABSTRACT: Direct nickel-catalyzed alkylation of chiral *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones using a commercially available nickel(II) complex, $(Me_3P)_2NiCl_2$, has been developed for tropylium and trityl tetrafluoroborate salts. The reaction provides a single diastereomer of the corresponding adducts in good to high yields, which, in turn, can be easily converted into a wide array of enantiomerically pure compounds that are difficult to obtain by other asymmetric procedures.



The stereoselective alkylation of metal enolates is one of the most significant methods to construct the carbon backbone of chiral compounds.[1] Particularly, the alkylations of lithium enolates from chiral *N*-acyl-1,3-oxazolidin-2-ones[2] or *N*-acylpseudoephedrines[3] are among the most successful and reliable approaches to the stereoselective construction of carbon−carbon bonds and have been largely employed in the synthesis of biologically active products.[4] Besides such well-established procedures, the better understanding of the structure and the reactivity of lithium enolates achieved during the last decades has revealed clues to tackle increasingly complicated challenges.[5,6] Parallel to these achievements, emphasis on asymmetric and catalytic transformations has also stimulated the development of insightful phase-transfer alkylation reactions.[7] However, different these methods may seem, they all feature the S_N2 addition of a chiral enolate to a suitable electrophile, preferentially an activated haloalkane, which restricts their scope and makes it therefore desirable to devise new approaches to prepare more elaborate or sterically hindered compounds.

In this context, methods based on an S_N1-like mechanism may be regarded as an appealing alternative. Highly enantioselective palladium- and iridium-catalyzed allylations of ketone enolates, in which the chiral cationic allyl−metal complex determines the stereochemical outcome of the addition, are proof of the synthetic potential of such an approach.[8−10] The opposite strategy, which involves the addition of a chiral nucleophile to a cationic intermediate, has also proved to be successful. Indeed, Evans demonstrated that titanium(IV) enolates could undergo reaction with orthoesters, acetals, and alkyl halides with a predisposition toward S_N1-like transformations.[11] This and subsequent contributions took advantage of heteroatom-stabilized intermediates,[12−14] but parallel transformations involving simple carbenium intermediates have also been described more recently. For instance, Jacobsen reported the enantioselective α-alkylation of aldehydes catalyzed by aminothiourea derivatives via an S_N1 pathway,[15] whereas the groups of Melchiorre[16] and Cozzi[17] have firmly established the feasibility of asymmetric organocatalytic alkylation of aldehydes through S_N1-type additions of chiral enamines to carbenium intermediates.[18] In contrast, similar procedures based on chiral metal enolates have been hardly reported, and most of them require activated carbonyl groups.[19,20]

As part of our studies aimed at the development of new catalytic and stereoselective carbon−carbon bond-forming reactions,[21] we have recently described a nickel-catalyzed alkylation of chiral *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones with diarylmethyl methyl ethers, which provide the corresponding adducts in high yields and with absolute stereocontrol.[22] Considering that the reaction involves the addition of a nickel(II) enolate to a cationic intermediate generated in situ, we thus envisaged that a related procedure based on the direct addition to naked carbenium cations[23] would avoid the need to activate the electrophile, greatly simplifying the experimental procedure and attaining a more atom-economic process, and might also provide a way to introduce sterically hindered groups, a challenge that still remains elusive. Herein, we describe the direct and diastereoselective alkylation of *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones with tropylium and trityl carbenium salts catalyzed by a commercially available nickel(II) complex, $(Me_3P)_2NiCl_2$, and subsequent conversion of the resultant adducts into enantiomerically pure derivatives (Scheme 1).

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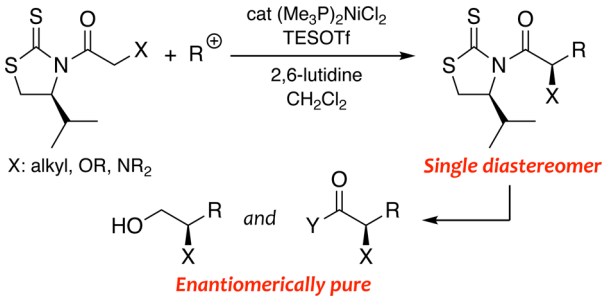
Scheme 1. Synthesis of Enantiomerically Pure Compounds by Direct and Stereoselective α-Alkylation of Chiral *N*-Acyl Thiazolidinethiones Catalyzed by a Nickel(II) Complex

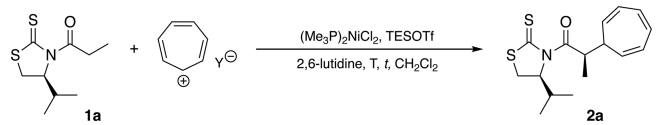


Applying small changes to the conditions previously employed[21,22] where the electrophile required activation, we initially assessed the addition of (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**1a**) to the stable tropylium cation, a model for naked carbenium ions, promoted by $(Me_3P)_2NiCl_2$ in the presence of 2,6-lutidine. Remarkably, this nickel(II) complex is structurally simple, robust, and can be handled without any special care; furthermore, this is easily activated in the reaction mixture by TESOTf to form the true catalyst, $(Me_3P)_2Ni(OTf)_2$. Preliminary experiments using tropylium tetrafluoroborate, $[C_7H_7]$ BF_4,[24] indicated that the addition was not affected significantly by the quantity of the electrophile, whereas, on the contrary, an increase of the reaction temperature had a detrimental influence on the conversion (compare entries 1−5 in Table 1). Then, we focused on the effect of the reaction time. We were pleased to observe that a single diastereomer of adduct **2a** was isolated in an 83% yield after 4 h (entry 6 in Table 1); further increases of the reaction time had little effect on the conversion (compare entries 6−8 in Table 1). Finally, reducing the catalyst loading to 5 mol % afforded **2a** with a slightly lower isolated yield than with double the catalyst (entries 9 and 10 in Table 1), but pushing the catalyst loading further down to 2.5 mol % produced a sharp decrease in the conversion (entries 11 and 12 in Table 1). As the poor solubility of the tropylium tetrafluoroborate raised some concerns, we also evaluated parallel additions of **1a** to more soluble tropylium bis(trifluorosulfonyl)amide, $[C_7H_7]$ NTf_2.[19a] The results were comparable to those previously obtained (entries 13 and 14 in Table 1), which proved that the use of $[C_7H_7]$ NTf_2 instead of less soluble but commercially available $[C_7H_7]$ BF_4 had no advantage even lowering the conversion slightly.

Once we had established the optimal conditions for the alkylation of **1a**, we proceeded to analyze the scope of the reaction by varying the side chain of the *N*-acyl thiazolidinethione and testing compatibility of the reaction with a large variety of functional groups. Remarkably, just one diastereomer was observed for all the screened substrates shown in Scheme 2. Increasing the steric bulk of X from **1a** (X = Me) to **1d** (X = *i*-Pr) induced a slight decrease of the yield, and alkylated products **2a** and **2d** were isolated in 83 and 68% yield, respectively. Lengthening and adding unsaturation in **1e** and **1f** or an ester group in **1g** had little effect on the yield, and the corresponding adducts **2e−g** were isolated in yields up to 81%. Even hetero-substituted enolates from **1h** and **1i** afforded the α-aza and α-oxy derivatives **2h** and **2i** in reasonably good yields. Moreover, X-ray diffraction analyses of crystalline adducts **2d** and **2h** firmly established the configuration of the new Cα-stereocenter (see Supporting Information).[25] All together, these achievements demonstrate that the nickel(II)-mediated direct catalytic alkylation of a broad array of *N*-acyl thiazolidinethiones **1**, with the naked tropylium carbenium ion, is a highly stereoselective procedure that permits you to obtain a single diastereomer of the corresponding adducts **2** in moderate to good yields under simple experimental conditions.

Taking advantage of the easy removal of the chiral scaffold,[26] we next converted adduct **2f** into various enantiomerically pure derivatives under mild experimental conditions, as represented in Scheme 3. Thereby, reduction of **2f** with $NaBH_4$ afforded alcohol **3f** in an 86% yield. In turn, ester **4f**, thioester **5f**, and morpholine amide **6f** were isolated in yields of 82−90% through treatment of **2f** with methanol, dodecanethiol, and morpholine, respectively. Finally, the thiazolidinethione was

Table 1. Direct and Catalytic α-Alkylation of *N*-Propanoyl Thiazolidinethione 1a with Tropylium Salts



entry	$(Me_3P)_2NiCl_2$ (mol %)	electrophile	equiv	*T* (°C)	*t* (h)	conversion[a] (yield)[b] (%)
1	10	$[C_7H_7]$ BF_4	1.1	−20	2	69
2	10	$[C_7H_7]$ BF_4	1.3	−20	2	73
3	10	$[C_7H_7]$ BF_4	1.5	−20	2	70
4	10	$[C_7H_7]$ BF_4	1.1	0	2	48
5	10	$[C_7H_7]$ BF_4	1.5	0	2	43
6	10	$[C_7H_7]$ BF_4	1.1	−20	4	88 (83)
7	10	$[C_7H_7]$ BF_4	1.5	−20	6	88
8	10	$[C_7H_7]$ BF_4	1.1	−20	15	84
9	5	$[C_7H_7]$ BF_4	1.1	−20	4	77 (71)
10	5	$[C_7H_7]$ BF_4	1.1	−20	15	81
11	2.5	$[C_7H_7]$ BF_4	1.1	−20	4	39
12	2.5	$[C_7H_7]$ BF_4	1.1	−20	15	43
13	10	$[C_7H_7]$ NTf_2	1.1	−20	2	63
14	10	$[C_7H_7]$ NTf_2	1.5	−20	2	58

[a]Established by ^1H NMR analysis of the reaction mixtures. [b]Isolated yield after chromatographic purification.

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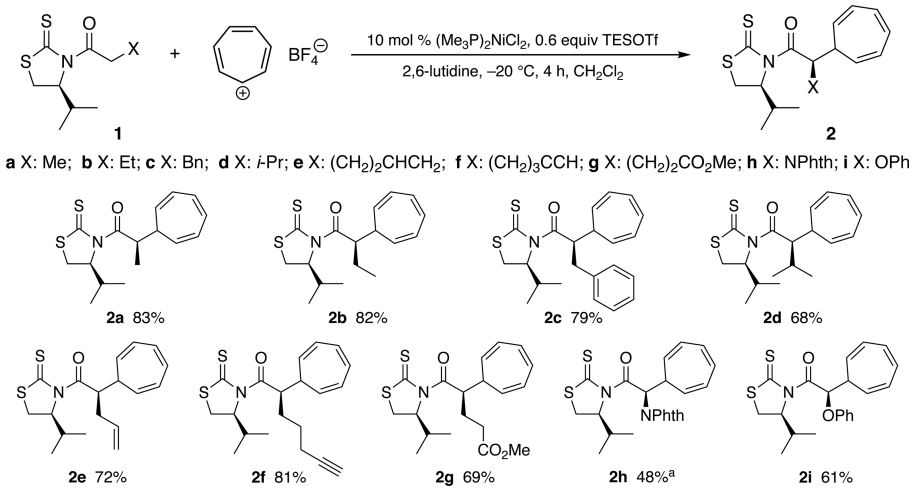
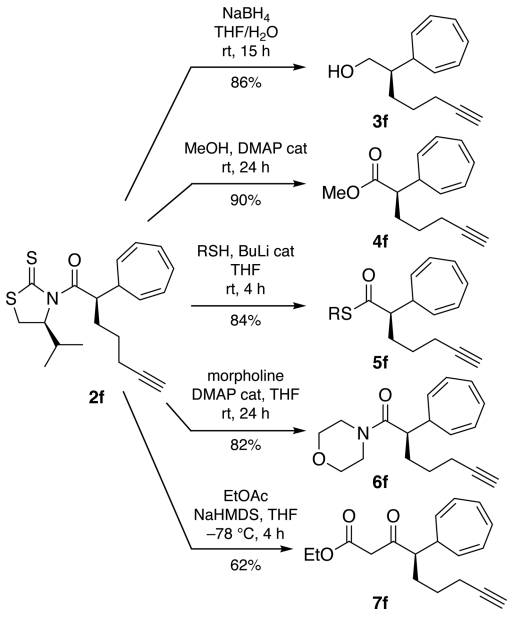
Scheme 2. Direct and Catalytic α-Alkylation of *N*-Acyl Thiazolidinethiones 1 with $[C_7H_7]$ BF_4



[a]20 mol % of catalyst was used.

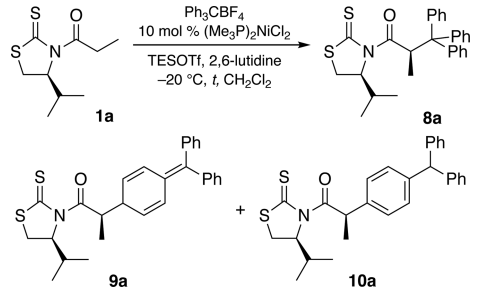
Scheme 3. Removal of the Chiral Auxiliary



displaced by the sodium enolate of ethyl acetate to deliver β-keto ester **7f** in a 62% yield. Noticeably, the conjugated triene from the tropylium cation did not undergo any rearrangement during the alkylation step or the removal of the chiral auxiliary. Indeed, derivatives **3f**–**7f** were all obtained, keeping intact the conjugated triene and the terminal triple bond, which highlights the synthetic potential of the overall procedure to prepare enantiomerically pure compounds containing a tropylium group. These sorts of intermediates may be used in the total synthesis of xanthanolides,[27] a large group of natural products whose structure contains a fused seven/five bicyclic system and features a remarkable range of biological properties.[28]

Finally, we moved to tackle a more challenging alkylating agent such as the trityl cation. The trityl group is commonly used to protect alcohols,[29] but it has rarely been employed in the stereoselective construction of carbon–carbon bonds because of its bulkiness, which makes it non-amenable to current alkylation methods. Thus, we envisaged that the experimental procedure optimized for tropylium tetrafluoroborate might be used to alkylate **1a** with trityl tetrafluoroborate, Ph_3CBF_4. Initial experiments were disappointing, with the desired alkylated adduct **8a** only isolated in low and somewhat variable yields. However, a careful analysis of the reaction mixtures showed that most of the starting material **1a** disappeared to produce **8a** and two other products, **9a** and **10a**. As shown in Table 2, these do not come from the addition

Table 2. Direct and Catalytic Alkylation of *N*-Propanoyl Thiazolidinethione 1a with Trityl Tetrafluoroborate



entry	t (h)	ratio[a] **8a**/**9a**/**10a**	yield of **8a**[b] (%)
1	4	25:60:15	22
2	15	45:30:25	40
3	30	65:10:25	57

[a]Established by ^{1}H NMR analysis of the reaction mixtures. [b]Isolated yield after chromatographic purification.

to the central carbon but to one of the phenyl groups. Indeed, **9a** contains a fully conjugated system that results directly from the nucleophilic attack of the enolate to the *para* position of a phenyl group. In turn, this undergoes a rearrangement to form **10a** to fully recover the aromatic character of the phenyl groups. As summarized in Table 2, the composition of the mixture changed dramatically with time, so the simple stirring of the reaction mixture for 30 h permitted the isolation of the desired adduct **8a** in a 57% yield. Further extensions of the reaction time did not increase this yield significantly.

Interestingly, submission of **9a** to the initial reaction conditions without any cation afforded the alkylated adduct **8a** and the fully aromatic compound **10a**. This proves that the changes in the composition of the mixtures summarized in

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Scheme 4. S_N1 Alkylation of 1a with a Trityl Salt Catalyzed by a Nickel(II) Complex

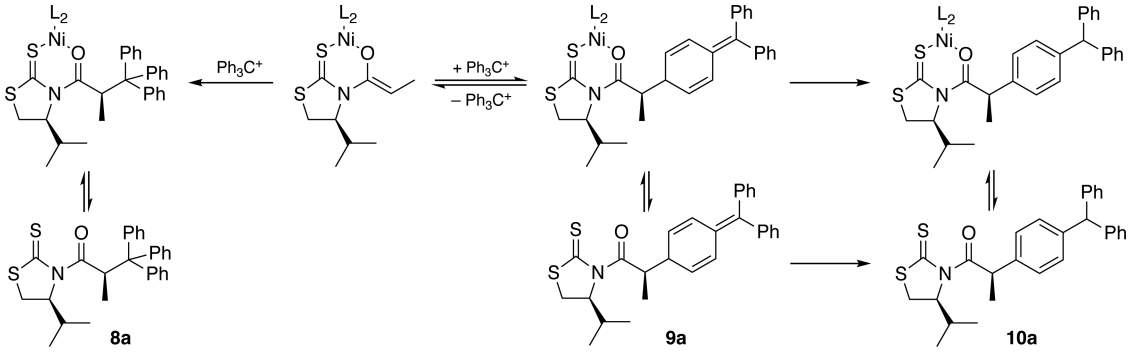

Table 2 are due to the reactivity of **9a**. Indeed, the central ring in **9a** tends to recover the aromatic character through a simple rearrangement, which produces **10a**, or by decomposing back into trityl cation and the nickel(II) enolate, which can eventually react to give **8a**. Therefore, the addition of the enolate to the *para* position to form **9a** is a reversible step, which is rare and only possible due to the stability of the trityl cation. The entire mechanism represented in Scheme 4 accounts for these results and also suggests that the nickel(II)-mediated alkylation of *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones can be applied to a large array of carbenium salts irrespective of their bulk provided that the reaction conditions are suitably tuned to the structure of the electrophile.

In conclusion, catalytic amounts of a commercially available nickel(II) complex, $(Me_3P)_2NiCl_2$, activated in situ with TESOTf, trigger a direct and completely diastereoselective alkylation of *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thiones with carbenium salts. The reaction is broadly tolerant of functionality and gives good yields in most cases with 10 mol % of nickel(II) complex. Furthermore, the straightforward removal of the chiral auxiliary under mild conditions provides concise access to a wide array of enantiomerically pure compounds that are difficult to prepare by other asymmetric procedures.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen with anhydrous solvents. The solvents and reagents were dried and purified, when necessary, according to standard procedures. All commercial reagents were used as received. Column chromatography was carried out under low-pressure (flash) conditions and performed on SDS silica gel 60 (35–70 μm). Analytical thin-layer chromatographies (TLC) were carried out on Merck silica gel 60 F254 plates and analyzed by UV (254 nm) and stained with phosphomolybdic acid or *p*-anisaldehyde. R_f values are approximate. Melting points were determined with a Stuart Scientific SMP10 or a Gallenkamp apparatus and are uncorrected. Specific rotations ($[\alpha]$) were determined at 589 nm and at 20 °C on a PerkinElmer 241 MC polarimeter. IR spectra (attenuated total reflectance, ATR) were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer, and only the more representative frequencies (ν) are reported. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are quoted in parts per million and referenced to internal TMS (δ 0.00 for ^{1}H NMR) or $CDCl_3$ (δ 77.0 for ^{13}C NMR); data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad (and their corresponding combinations) with coupling constants measured in Hz; when necessary, 2D techniques (COSY and HSQC) were also used to assist with structure elucidation. High-resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer with a TOF analyzer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

Preparation of *N*-Acyl Thiazolidinethiones. As previously reported, *N*-acyl thiazolidinethiones **1** were prepared by acylation of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione.[22,30]

*(S)-N-(6-Heptynoyl)-4-isopropyl-1,3-thiazolidine-2-thione (**1f**).* A solution of 6-heptynoic acid (693 mg, 5.5 mmol) in CH_2Cl_2 (5 mL) was added via cannula to a solution of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (805 mg, 5.0 mmol), EDC·HCl (1.15 g, 6.0 mmol), and DMAP (31 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) at room temperature. The resultant mixture was stirred at room temperature for 8 h, diluted in CH_2Cl_2 (20 mL), and washed with 2 M HCl (20 mL), 2 M NaOH (20 mL), and brine (20 mL). The organic phase was then dried ($MgSO_4$) and concentrated. The crude mixture was purified by column chromatography (70:30 CH_2Cl_2/hexanes) to afford 1.229 g (91% yield) of (*S*)-*N*-(6-heptynoyl)-4-isopropyl-1,3-thiazolidine-2-thione (**1f**) as a yellow oil. R_f 0.50 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +345.5 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3234, 2955, 2867, 1689, 1461, 1363, 1255, 1144, 1030, 631 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (1H, ddd, *J* = 8.0, 6.2, 1.2 Hz), 3.50 (1H, dd, *J* = 11.5, 8.0 Hz), 3.38, (1H, ddd, *J* = 17.2, 8.5, 6.0 Hz), 3.17 (1H, ddd, *J* = 17.2, 8.5, 6.3 Hz), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz), 2.42–2.29 (1H, m), 2.22 (2H, td, *J* = 7.1, 2.7 Hz), 1.95 (1H, t, *J* = 2.7 Hz), 1.90–1.70 (2H, m), 1.65–1.55 (2H, m), 1.06 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 173.6 (C), 84.0 (C), 71.6 (CH), 68.6 (CH), 37.7 (CH_2), 30.8 (CH_2), 30.4 (CH), 27.8 (CH_2), 23.9 (CH_2), 19.0 (CH_3), 18.3 (CH_3), 17.7 (CH_2). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{13}H_{20}NOS_2$ 270.0981; found 270.0974.

*(S)-4-Isopropyl-N-(2-phenoxyacetyl)-1,3-thiazolidine-2-thione (**1i**).* A 2.5 M solution of *n*-BuLi in hexanes (4.4 mL, 11.0 mmol) was added dropwise to a solution of (*S*)-4-isopropyl-1,3-thiazolidine-2-thione (1.61 g, 10.0 mmol) in THF (7 mL) at −78 °C. The resultant mixture was stirred for 15 min, and 2-phenoxyacetyl chloride (1.8 mL, 13.0 mmol) was carefully added. The reaction mixture was stirred for 5 min at −78 °C and 1.5 h at room temperature, cooled to 0 °C, and quenched with saturated NH_4Cl (2 mL) and water (5 mL). This mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with 2 M NaOH (3 × 10 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (50:50 hexanes/CH_2Cl_2) to afford 2.80 g (9.5 mmol, 95% yield) of (*S*)-4-isopropyl-*N*-(2-phenoxyacetyl)-1,3-thiazolidine-2-thione (**1i**) as a yellow solid. Mp 80–83 °C. R_f 0.35 (50:50 hexanes/CH_2Cl_2). $[\alpha]_D^{20}$ +235.1 (*c* 1.00, $CHCl_3$). IR (ATR) ν 2958, 1701, 1594, 1492, 1363, 1239, 1166, 1084, 1036, 751, 688 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30–6.90 (5H, m), 5.59 (1H, d, *J* = 17.4 Hz), 5.49 (1H, d, *J* = 17.4 Hz), 5.20 (1H, ddd, *J* = 8.1, 6.1, 1.1 Hz), 3.64 (1H, dd, *J* = 11.6, 8.1 Hz), 3.12 (1H, dd, *J* = 11.6, 1.1 Hz), 2.46–2.35 (1H, m), 1.09 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 169.2 (C), 157.7 (C), 129.6 (CH), 121.6 (CH), 114.8 (CH), 71.5 (CH), 69.7 (CH_2), 31.5 (CH_2), 30.8 (CH), 19.0 (CH_3), 17.6 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{14}H_{18}NO_2S_2$ 296.0773, found 296.0786.

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General Procedure for the Alkylation of 1. Solid $(Me_3P)_2NiCl_2$ (14.2 mg, 50 μmol, 10 mol %) was added to a solution of thioimide **1** (0.5 mmol) and tropylium tetrafluoroborate (98 mg, 0.55 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The resulting dark red suspension was purged with N_2 and then cooled to −20 °C. Next, TESOTf (68 μL, 0.3 mmol) was added followed by 2,6-lutidine (88 μL, 0.75 mmol) after 4 min. The resultant mixture was stirred at −20 °C for 4 h. The reaction was quenched with saturated NH_4Cl (1.2 mL) and diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. ^1H NMR analysis of the crude product showed the presence of a single diastereomer of the corresponding alkylation product **2**. The crude was purified by flash column chromatography to afford the desired alkylated product **2**.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2a**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione **1a** (108 mg, 0.5 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 128 mg (0.42 mmol, 83% yield) of **2a** as a yellow oil. R_f 0.70 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +225.0 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3011, 2959, 2925, 2870, 1683, 1457, 1360, 1253, 1231, 1145, cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68−6.62 (2H, m), 6.25−6.17 (2H, m), 5.32 (2H, dt, *J* = 9.4, 5.7 Hz), 5.21 (1H, ddd, *J* = 8.1, 5.9, 1.2 Hz), 5.09 (1H, dq, *J* = 8.4, 6.9 Hz), 3.47 (1H, dd, *J* = 11.5, 8.1 Hz), 2.98 (1H, dd, *J* = 11.5, 1.2 Hz), 2.23 (1H, dtt, *J* = 8.4, 6.1, 1.2 Hz), 1.27 (3H, d, *J* = 6.9 Hz), 1.04 (3H, d, *J* = 6.9 Hz), 0.97 (3H, t, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.7 (C), 176.9 (C), 131.0 (CH), 130.6 (CH), 125.4 (CH), 125.0 (CH), 124.6 (CH), 122.6 (CH), 71.9 (CH), 42.0 (CH), 39.6 (CH), 30.8 (CH), 29.7 (CH_2), 19.2 (CH_3), 17.6 (CH_3), 15.1 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{16}H_{22}NOS_2$ 308.1137, found 308.1139.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)butanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2b**).* It was prepared according to the general procedure from (*S*)-*N*-butanoyl-4-isopropyl-1,3-thiazolidine-2-thione **1b** (116 mg, 0.5 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 132 mg (0.41 mmol, 82% yield) of **2b** as a yellow oil. R_f 0.80 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +324.8 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3012, 2958, 2929, 2869, 1682, 1454, 1359, 1305, 1115, 1090, 1030, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68−6.62 (2H, m), 6.23−6.16 (2H, m), 5.41−5.38 (1H, m), 5.32−5.28 (1H, m), 5.21−5.18 (2H, m), 3.47 (1H, dd, *J* = 11.5, 7.9 Hz), 3.01 (1H, dd, *J* = 11.5, 1.0 Hz), 2.40−2.30 (1H, m), 2.11 (1H, dtt, *J* = 8.8, 6.0, 1.3 Hz), 1.87−1.75 (2H, m), 1.06 (3H, d, *J* = 6.9 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 0.90 (3H, t, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.2 (C), 176.4 (C), 131.0 (CH), 130.6 (CH), 125.2 (CH), 125.0 (CH), 124.4 (CH), 122.7 (CH), 72.0 (CH), 45.8 (CH), 41.2 (CH), 30.8 (CH), 30.6 (CH_2), 23.8 (CH_2), 19.2 (CH_3), 17.9 (CH_3), 11.2 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{17}H_{24}NOS_2$ 322.1294, found 322.1282.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-3-phenylpropanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2c**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(3-phenylpropanoyl)-1,3-thiazolidine-2-thione **1c** (146 mg, 0.5 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 151 mg (0.39 mmol, 79% yield) of **2c** as a yellow oil. R_f 0.80 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +415.2 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3012, 2961, 2872, 1685, 1362, 1251, 1147, 1036, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.21 (5H, m), 6.71−6.69 (2H, m), 6.30−6.26 (1H, m), 6.22−6.18 (1H, m), 5.65−5.55 (2H, m), 5.41 (1H, dd, *J* = 9.4, 5.8 Hz), 4.51 (1H, t, *J* = 7.2 Hz), 3.27 (1H, dd, *J* = 13.2, 4.8 Hz), 2.74 (1H, dd, *J* = 13.2, 11.3 Hz), 2.64 (1H, d, *J* = 11.2 Hz), 2.50 (1H, dd, *J* = 11.2, 7.2 Hz), 2.30−2.15 (1H, m), 2.09 (1H, dt, *J* = 10.0, 5.9 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 0.90 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 204.1 (C), 176.4 (C), 138.5 (C), 131.2 (CH), 130.7 (CH), 128.7 (CH), 128.5 (CH), 126.6 (CH), 125.4 (CH), 125.1 (CH), 123.9 (CH), 122.6 (CH), 72.1 (CH), 46.2 (CH), 42.5 (CH), 39.1 (CH_2), 31.2 (CH_2), 30.5 (CH), 19.2 (CH_3), 18.3 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{22}H_{26}NOS_2$ 384.1450, found 384.1441.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-3-methylbutanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2d**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(3-methylbutanoyl)-1,3-thiazolidine-2-thione (122 mg, 0.5 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 118 mg (0.35 mmol, 70% yield) of 2d as a yellow solid. Mp 89−91 °C. R_f 0.70 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +488.8 (*c* 1.00, $CHCl_3$). IR (ATR) ν 2958, 2869, 1688, 1463, 1337, 1248, 1229, 1147, 1115, 1020, 700, 684 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70−6.64 (2H, m), 6.22−6.16 (2H, m), 5.51 (1H, dd, *J* = 9.3, 5.9 Hz), 5.32−5.26 (2H, m), 5.14−5.09 (1H, m), 3.47 (1H, dd, *J* = 11.5, 7.6 Hz), 3.04 (1H, dd, *J* = 11.5, 0.8 Hz), 2.47−2.35 (1H, m), 2.33−2.20 (1H, m), 2.05−1.98 (1H, m), 1.09 (3H, d, *J* = 6.8 Hz), 1.01 (3H, d, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.9 (C), 175.9 (C), 130.9 (CH), 130.5 (CH), 124.7 (CH), 124.6 (CH), 123.6 (CH), 122.8 (CH), 72.1 (CH), 48.9 (CH), 40.4 (CH), 31.2 (CH_2), 30.8 (CH), 30.6 (CH), 20.6 (CH_3), 19.3 (CH_3), 19.0 (CH_3), 18.2 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{18}H_{26}NOS_2$ 336.1450, found 336.1454.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-4-pentenoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2e**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(4-pentenoyl)-1,3-thiazolidine-2-thione **1e** (123 mg, 0.50 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 131 mg (0.36 mmol, 72% yield) of **2e** as a yellow oil. R_f 0.60 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +297.6 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3005, 2958, 2926, 2869, 1682, 1356, 1245, 1144, 1087, 1030, 912, 836, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70−6.62 (2H, m), 6.26−6.16 (2H, m), 5.80 (1H, dddd, *J* = 17.1, 10.2, 8.4, 5.9 Hz), 5.43 (1H, dd, *J* = 9.4, 5.9 Hz), 5.34−5.27 (2H, m), 5.09−5.00 (3H, m), 3.43 (1H, dd, *J* = 11.4, 7.8 Hz), 2.99 (1H, dd, *J* = 11.4, 0.9 Hz), 2.57 (1H, dddt, *J* = 14.1, 5.9, 4.3, 1.6 Hz), 2.46−2.42 (1H, m), 2.40−2.30 (1H, m), 2.20−2.13 (1H, m), 1.05 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.5 (C), 175.8 (C), 134.9 (CH), 131.1 (CH), 130.6 (CH), 125.4 (CH), 125.1 (CH), 124.2 (CH), 122.5 (CH), 117.1 (CH_2), 72.2 (CH), 44.4 (CH), 41.3 (CH), 35.7 (CH_2), 30.9 (CH_2), 30.8 (CH), 19.2 (CH_3), 18.0 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{18}H_{24}NOS_2$ 334.1294, found 334.1296.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptynoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2f**).* It was prepared according to the general procedure from (*S*)-*N*-(6-heptynoyl)-4-isopropyl-1,3-thiazolidine-2-thione (135 mg, 0.50 mmol). Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 155 mg (0.41 mmol, 82% yield) of **2f** as a yellow oil. R_f 0.60 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +292.2 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3290, 3012, 2958, 2926, 2863, 1682, 1467, 1359, 1235, 1144, 1090, 1023, 738, 700 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68−6.62 (2H, m), 6.24−6.17 (2H, m), 5.48−5.31 (1H, m), 5.34−5.29 (1H, m), 5.27−5.22 (1H, m), 5.22 (1H, ddd, *J* = 7.9, 4.3, 1.2 Hz), 3.49 (1H, dd, *J* = 11.5, 7.9 Hz), 3.01 (1H, dd, *J* = 11.5, 1.2 Hz), 2.40−2.27 (1H, dq, *J* = 13.6, 6.8 Hz), 2.20 (2H, td, *J* = 7.0, 2.6 Hz), 2.11 (1H, dtt, *J* = 8.4, 5.9, 1.3 Hz), 1.97−1.94 (1H, m), 1.91−1.87 (2H, m), 1.56−1.46 (2H, m), 1.04 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.1 (C), 176.1 (C), 131.1 (CH), 130.7 (CH), 125.3 (CH), 125.1 (CH), 124.1 (CH), 122.4 (CH), 83.7 (C), 72.0 (CH), 68.8 (CH), 44.1 (CH), 41.5 (CH), 30.8 (CH), 30.4 (CH_2), 29.5 (CH_2), 25.8 (CH_2), 19.2 (CH_3), 18.5 (CH_2), 17.8 (CH_3). HRMS (+ESI): *m*/*z* calcd for $[M + H]^+$ $C_{20}H_{26}NOS_2$ 360.1450, found 360.1455.

*(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-4-methoxycarbonylbutanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2g**).* It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(4-methoxycarbonylbutanoyl)-1,3-thiazolidine-2-thione **1g** (144 mg, 0.50 mmol). Purification of the crude product by column chromatography (80:20 hexanes/EtOAc) afforded 131 mg (0.35 mmol, 69% yield) of **2g** as a yellow oil. R_f 0.40 (80:20 hexanes/EtOAc). $[\alpha]_D^{20}$ +221.9 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3012, 2958, 2869, 1729, 1435, 1359, 1239, 1090, 1030, 697 cm^{-1}. ^1H NMR

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($CDCl_3$, 400 MHz) δ 6.70−6.60 (2H, m), 6.25−6.15 (2H, m), 5.40 (1H, dd, J = 9.4, 5.9 Hz), 5.32 (1H, dd, J = 9.4, 6.1 Hz), 5.27 (1H, td, J = 9.5, 4.3 Hz), 5.20 (1H, ddd, J = 7.7, 6.3, 1.0 Hz), 3.67 (3H, s), 3.54 (1H, dd, J = 11.4, 7.9 Hz), 3.00 (1H, dd, J = 11.4, 1.1 Hz), 2.40−2.25 (3H, m), 2.20−2.05 (3H, m), 1.04 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.2 (C), 175.7 (C), 173.3 (C), 131.1 (CH), 130.7 (CH), 125.5 (CH), 125.2 (CH), 123.8 (CH), 122.1 (CH), 72.0 (CH), 51.7 (CH_3), 43.5 (CH), 41.4 (CH), 31.3 (CH_2), 30.7 (CH), 30.4 (CH_2), 25.4 (CH_2), 19.2 (CH_3), 17.9 (CH_3). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{19}H_{26}NO_3S_2$ 380.1349, found 380.1357.

(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-N,N-phthaloyl-2-aminoacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2h**). It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(*N*,*N*-phthaloyl-2-aminoacetyl)-1,3-thiazolidine-2-thione **1h** (348 mg, 1.0 mmol), $(Me_3P)_2NiCl_2$ (56.4 mg, 0.20 mmol, 20 mol %), tropylium tetrafluoroborate (196 mg, 1.10 mmol), TESOTf (115 μL, 0.50 mmol), and 2,6-lutidine (175 μL, 1.5 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 4 h at −20 °C. Purification of the crude product by column chromatography (70:30 CH_2Cl_2/hexanes) afforded 209 mg (0.48 mmol, 48% yield) of **2h** as a yellow solid. Mp 134−138 °C. R_f 0.40 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +253.2 (c 1.00, $CHCl_3$). IR (ATR) ν 2958, 1770, 1707, 1467, 1375, 1261, 1163, 716, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86−7.84 (2H, m), 7.76−7.74 (2H, m), 6.71−6.64 (2H, m), 6.42 (1H, d, J = 8.1 Hz), 6.23−6.26 (1H, m), 6.20−6.16 (1H, m), 5.61−5.57 (1H, m) 5.33−5.29 (1H, m), 4.82 (1H, ddd, J = 7.5, 6.3, 0.9 Hz), 3.40 (1H, dd, J = 11.2, 7.5 Hz), 2.98 (1H, dd, J = 11.2, 0.9 Hz), 2.75 (1H, dtt, J = 8.1, 6.2, 1.1 Hz), 2.52−2.40 (1H, m), 1.05 (3H, d, J = 6.9 Hz), 1.03 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 201.8 (C), 169.5 (C), 167.7 (C), 134.5 (CH), 131.1 (CH), 131.0 (CH), 130.9 (CH), 126.2 (CH), 124.6 (CH), 123.6 (CH), 123.4 (CH), 120.6 (CH), 74.2 (CH), 54.2 (CH), 41.5 (CH), 32.2 (CH_2), 31.2 (CH), 19.2 (CH_3), 18.0 (CH_3). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{23}H_{23}N_2O_3S_2$ 439.1145, found 439.1128.

(S)-N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-2-phenoxyacetyl]-4-isopropyl-1,3-thiazolidine-2-thione (**2i**). It was prepared according to the general procedure from (*S*)-4-isopropyl-*N*-(2-phenoxyacetyl)-1,3-thiazolidine-2-thione **1i** (148 mg, 0.50 mmol). Purification of the crude product by column chromatography (60:40 CH_2Cl_2/hexanes) afforded 118 mg (0.31 mmol, 61% yield) of **2i** as a yellow oil. R_f 0.65 (60:40 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +69.3 (c 1.00, $CHCl_3$). IR (ATR) ν 3025, 2955, 2870, 1698, 1597, 1587, 1489, 1363, 1236, 1157, 1084, 748, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.27 (2H, m, 2H), 7.18 (1H, d, J = 2.7 Hz), 7.02−6.96 (1H, m), 6.95−6.90 (2H, m), 6.72−6.62 (2H, m), 6.31−6.23 (2H, m), 5.74 (1H, dd, J = 9.5, 5.6 Hz), 5.42 (1H, dd, J = 9.4, 5.4 Hz), 5.30 (1H, ddd, J = 8.8, 5.4, 1.6 Hz), 3.52 (1H, dd, J = 11.6, 8.8 Hz), 3.01 (1H, dd, J = 11.6, 1.6 Hz), 2.49−2.42 (1H, m), 2.26−2.13 (1H, m), 0.91 (3H, d, J = 6.8 Hz), 0.90 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.0 (C), 171.1 (C), 157.7 (C), 131.0 (CH), 130.8 (CH), 129.7 (CH), 125.5 (CH), 125.4 (CH), 122.1 (CH), 121.7 (CH), 120.0 (CH), 115.2 (CH), 76.1 (CH), 71.7 (CH), 41.7 (CH), 30.7 (CH), 30.2 (CH_2), 19.0 (CH_3), 17.0 (CH_3). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{21}H_{24}NO_2S_2$ 386.1243, found 386.1247.

Removal of the Chiral Auxiliary. *(R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptyn-1-ol* (**3f**). A mixture of **2f** (180 mg, 0.5 mmol) and $NaBH_4$ (94.5 mg, 2.5 mmol) in THF/H_2O (10 mL/0.1 mL) was stirred for 15 h at room temperature. The mixture was diluted in Et_2O (20 mL) and washed with 1 M NaOH (3 × 20 mL), H_2O (20 mL), and brine (20 mL). The organic layer was then dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (CH_2Cl_2) afforded 87 mg (86% yield) of pure alcohol **3f** as a colorless oil. R_f 0.25 (CH_2Cl_2). $[\alpha]_D^{20}$ +10.1 (c 1.00, $CHCl_3$). IR (ATR) ν 3364 (br), 3294, 3009, 2923, 2866, 1027, 734, 701, 628 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.69−6.65 (2H, m), 6.26−6.19 (2H, m), 5.35−5.28 (2H, m), 3.80 (2H, t, J = 5.2 Hz), 2.25−2.20 (2H, m), 1.96 (1H, t, J = 2.7 Hz), 1.90−1.82 (1H, m), 1.76−1.54 (5H, m), 1.23 (1H, t, J = 5.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 130.9 (CH), 130.7 (CH), 125.1 (2 × CH), 123.7 (CH), 123.6 (CH), 84.4 (C), 68.6 (CH), 63.4 (CH_2), 41.6 (CH), 40.4 (CH), 27.9 (CH_2), 26.1 (CH_2), 18.7 (CH_2). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{14}H_{19}O$ 203.1430, found 203.1436.

Acidification of the aqueous layer using HCl (until pH 1) and subsequent extraction with CH_2Cl_2 (3 × 20 mL) gave 67 mg (84%) of recovered chiral thiazolidinethione.

Methyl (R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptynoate (**4f**). A solution of **2f** (180 mg, 0.5 mmol) and DMAP (25 mg, 0.2 mmol) in MeOH (5 mL) was stirred for 24 h at room temperature. The solvent was removed, and the resulting crude mixture was dissolved in Et_2O (20 mL). The ethereal solution was washed with 1 M NaOH (3 × 20 mL) and H_2O (20 mL), and the organic layer was dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (50:50 hexanes/CH_2Cl_2) yielded 103 mg (90% yield) of ester **4f** as a colorless oil. R_f 0.60 (50:50 hexanes/CH_2Cl_2). $[\alpha]_D^{20}$ +24.2 (c 1.00, $CHCl_3$). IR (ATR) ν 3291, 3009, 2945, 2863, 1729, 1432, 1194, 1154, 702, 635 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.69−6.63 (2H, m), 6.25−6.17 (2H, m), 5.31−5.23 (2H, m), 3.71 (3H, s), 2.72 (1H, td, J = 9.7, 4.2 Hz), 2.21 (2H, td, J = 7.0, 2.7 Hz), 1.96 (1H, t, J = 2.7 Hz), 1.95−1.91 (1H, m), 1.87−1.73 (2H, m), 1.56−1.46 (2H, m). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.3 (C), 131.1 (CH), 130.8 (CH), 125.4 (CH), 125.3 (CH), 123.1 (CH), 122.9 (CH), 83.8 (C), 68.7 (CH), 51.6 (CH_3), 46.9 (CH), 41.3 (CH), 29.3 (CH_2), 26.2 (CH_2), 18.2 (CH_2). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{15}H_{19}O_2$ 231.1380, found 231.1381.

Acidification of the aqueous layer using HCl (until pH 1) and extraction with CH_2Cl_2 (3 × 20 mL) gave 71 mg (89%) of recovered chiral thiazolidinethione.

S-Dodecyl (R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptynethioate (**5f**). A 2.5 M solution of *n*-BuLi in hexanes (60 μL, 0.15 mmol) was added to a solution of dodecanethiol (360 μL, 1.5 mmol) in THF (3 mL) at 0 °C. The reaction was left 15 min before a solution of **2f** (180 mg, 0.5 mmol) in THF (2 mL) was added dropwise. The resultant mixture was stirred for 15 min at 0 °C and for 4 h at room temperature. The mixture was then diluted in H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (from 90:10 hexanes/CH_2Cl_2 to CH_2Cl_2) to afford 64 mg (80%) of recovered chiral auxiliary and 168 mg (84% yield) of thioester **5f** as a colorless oil. R_f 0.55 (70:30 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +19.5 (c 1.00, $CHCl_3$). IR (ATR) ν 3307, 3018, 2920, 2851, 1679, 1454, 964, 742, 698, 628 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.70−6.62 (2H, m), 6.27−6.15 (2H, m), 5.35 (1H, dd, J = 9.5, 6.0 Hz), 5.27 (1H, dd, J = 9.5, 6.0 Hz), 2.90 (2H, t, J = 7.3 Hz), 2.95−2.83 (1H, m), 2.26−2.16 (2H, m), 2.01−1.97 (1H, m), 1.96 (1H, t, J = 2.7 Hz), 1.91−1.75 (2H, m), 1.66−1.46 (4H, m), 1.41−1.21 (18H, m), 0.88 (3H, t, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.1 (C), 131.1 (CH), 130.8 (CH), 125.4 (CH), 125.3 (CH), 123.0 (CH), 122.5 (CH), 83.7 (C), 68.7 (CH), 55.1 (CH), 41.7 (CH), 31.9 (CH_2), 29.9 (CH_2), 29.6 (3 × CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 28.8 (CH_2), 25.9 (CH_2), 22.7 (CH_2), 18.3 (CH_2) 14.1 (CH_3). HRMS (+ESI): m/z calcd for $[M + NH_4]^+$ $C_{26}H_{44}NOS$ 418.3138, found 418.3138.

N-[(R)-2-(2,4,6-Cycloheptatrien-1-yl)-6-heptynoyl]morpholine (**6f**). Morpholine (130 μL, 1.5 mmol) was added dropwise to a solution of **2f** (180 mg, 0.5 mmol) and DMAP (50 mg, 0.4 mmol) in THF (10 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 24 h. The volatiles were removed to leave a crude mixture that was purified by column chromatography (from 50:50 hexanes/CH_2Cl_2 to 95:5 CH_2Cl_2/MeOH) to afford 63 mg (79%) of recovered chiral auxiliary and 116 mg (82% yield) of amide **6f** as a yellowish oil. R_f 0.50 (97.5:2.5 CH_2Cl_2/MeOH). $[\alpha]_D^{20}$ +2.0 (c 1.00, $CHCl_3$). IR (ATR) ν 3288, 3012, 2918, 2854, 1625, 1429, 1223, 1112, 1027, 701, 641 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.66−6.56 (m, 2H), 6.26 (1H, dd, J = 9.7, 5.5 Hz), 6.20 (1H, dd, J = 9.7, 4.8 Hz), 5.40 (1H, dd, J = 9.5, 7.2 Hz), 5.32 (1H, dd, J = 9.5, 7.0 Hz), 3.70−3.61 (6H, m), 3.49−3.43 (2H, m), 2.87 (1H, td, J = 9.6, 4.1 Hz), 2.55 (1H, dt, J = 9.6, 7.0 Hz), 2.19−2.12 (2H, m), 1.95 (1H, t, J = 2.6 Hz), 1.84−1.69 (2H, m), 1.56−1.44 (1H, m), 1.41−1.30 (1H, m). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.2 (C), 130.8 (CH), 130.5 (CH),

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125.9 (CH), 125.6 (CH), 124.5 (CH), 123.9 (CH), 83.9 (C), 68.7 (CH), 67.2 (CH_2), 66.9 (CH_2), 46.4 (CH_2), 42.2 (CH_2), 41.5 (CH), 39.8 (CH), 29.9 (CH_2), 26.1 (CH_2), 18.5 (CH_2). HRMS (+ESI): m/z calcd for $[M + H]^+$ $C_{18}H_{24}NO_2$ 286.1802, found 286.1803.

*Ethyl (R)-4-(2,4,6-Cycloheptatrien-1-yl)-3-oxo-8-nonynoate (**7f**).* A solution of EtOAc (0.1 mL, 1.0 mmol) and 1 M NaHMDS in THF (1 mL, 1.0 mmol) in THF (2.5 mL) was stirred for 1 h at −78 °C. A solution of **2f** (180 mg, 0.5 mmol) in THF (2.5 mL) was then added, and the resultant mixture was stirred for 4 h at −78 °C. The reaction was quenched with NH_4Cl (5 mL). The mixture was diluted with EtOAc (20 mL), washed with H_2O (20 mL), 1 M NaOH (2 × 20 mL), dried ($MgSO_4$), and concentrated. Purification by column chromatography (from 50:50 to 40:60 hexanes/CH_2Cl_2) of the residue yielded 88 mg (62% yield) of a ≈70:30 keto/enol mixture of β-keto ester **7f** as a colorless oil. R_f 0.45 (CH_2Cl_2). $[\alpha]_D^{20}$ +34.2 (*c* 1.00, $CHCl_3$). IR (ATR) ν 3291, 2980, 2933, 2863, 1742, 1704, 1641, 1622, 1492, 1226, 1144, 1207, 698, 634 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 12.12 (1H, s, *enol*), 6.71−6.63 (2H, m), 6.29−6.16 (2H, m), 5.32−5.18 (2H, m), 5.04 (1H, s, *enol*), 4.20 (2H, q, *J* = 7.0 Hz, *enol*), 4.18 (2H, q, *J* = 7.1 Hz), 3.46 (1H, d, *J* = 15.6 Hz), 3.38 (1H, d, *J* = 15.6 Hz), 2.94 (1H, td, *J* = 9.3, 4.3 Hz), 2.41−2.35 (1H, m, *enol*), 2.20 (2H, td, *J* = 7.0, 2.6 Hz), 2.06 (1H, dt, *J* = 9.3, 6.3 Hz), 1.96 (1H, t, *J* = 2.6 Hz), 1.90−1.79 (2H, m), 1.78−1.71 (1H, m, *enol*), 1.60−1.41 (2H, m), 1.31 (3H, t, *J* = 7.1 Hz, *enol*), 1.27 (3H, t, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ *keto* 205.2 (C), 166.9 (C), 131.0 (CH), 130.9 (CH), 125.8 (CH), 125.7 (CH), 123.1 (CH), 122.0 (CH), 83.6 (C), 68.9 (CH), 61.3 (CH_2), 53.2(CH_2), 48.4 (CH), 40.1 (CH), 28.1 (CH_2), 25.6 (CH_2), 18.3 (CH_2), 14.1 (CH_3); *enol* 178.8 (C), 172.4 (C), 131.0 (CH), 130.7 (CH), 125.3 (CH), 125.0 (CH), 123.6 (CH), 123.3 (CH), 91.3 (CH), 84.0 (C), 68.6 (CH), 60.1 (CH_2), 47.0 (CH), 41.4 (CH), 29.4 (CH_2), 26.0 (CH_2), 18.3 (CH_2), 14.2 (CH_3). HRMS (+ESI): m/z calcd for $[M + NH_4]^+$ $C_{18}H_{26}NO_3$ 304.1907, found 304.1906.

Acidification of the aqueous layer using HCl (until pH 1) and extraction with CH_2Cl_2 (3 × 20 mL) afforded 68 mg (85%) of recovered chiral thiazolidinethione.

Coupling with Trityl Cation. Solid $(Me_3P)_2NiCl_2$ (28.2 mg, 0.1 mmol, 10 mol %) was added to a solution of **1a** (217 mg, 1.0 mmol) and trityl tetrafluoroborate (396 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) at room temperature, and the resulting dark red suspension was cooled to −20 °C. Then, TESOTf (140 μL, 0.6 mmol) was added followed by 2,6-lutidine (180 μL, 1.5 mmol) after 4 min. The reaction mixture was stirred at −20 °C for 30 h.

The reaction was quenched with saturated NH_4Cl (2 mL) and diluted in H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. ^1H NMR analysis of the crude product showed a full conversion and a ≈65:10:25 **8a**/**9a**/**10a** mixture. This was then directly purified by column chromatography (60:40 hexanes/CH_2Cl_2) to yield 261 mg (0.57 mmol, 57% yield) of the alkylated adduct **8a** and 92 mg (0.20 mmol, 20% yield) of **10a**.

*(S)-4-Isopropyl-N-[(R)-2-(triphenylmethyl)propanoyl]-1,3-thiazolidine-2-thione (**8a**).* Yellow solid. Mp 190−192 °C. R_f 0.50 (60:40 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +185.0 (*c* 1.00, $CHCl_3$). IR (ATR) ν 2962, 2836, 1697, 1707, 1488, 1362, 1241, 1134 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.54−7.03 (16H, m), 5.07 (1H, ddd, *J* = 8.2, 5.3, 0.9 Hz), 3.32 (1H, dd, *J* = 11.5, 8.2 Hz), 2.90 (1H, dd, *J* = 11.5, 0.9 Hz), 2.10−2.00 (1H, m), 1.10 (3H, d, *J* = 7.2 Hz), 1.04 (3H, d, *J* = 6.9 Hz), 0.83 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.7 (C), 175.2 (C), 144.0 (C), 128.7 (CH), 127.7 (CH), 126.9 (CH) 72.2 (CH), 60.5 (C), 42.7 (CH), 30.7 (CH), 28.4 (CH_2), 19.0 (CH_3), 17.4 (CH_3), 16.6 (CH_3). HRMS (+ESI): m/z calcd for $C_{28}H_{30}NOS_2$ $[M + H]^+$ 460.1763; found 460.1767.

*(S)-N-[(R)-2-(4-Diphenylmethylene-2,5-cyclohexadien-1-yl)-propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**9a**).* Yellowish and unstable solid. R_f 0.50 (60:40 CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.23 (6H, m), 7.20−7.14 (4H, m), 6.66−6.54 (2H, m), 5.80−5.67 (2H, m), 5.34−5.29 (1H, m), 4.66 (1H, qd, *J* = 6.8, 3.4 Hz), 3.91−3.81 (1H, m), 3.51 (1H, dd, *J* = 11.5, 8.2 Hz), 3.00 (1H, dd, *J* = 11.5, 1.3 Hz), 2.38−2.22 (1H, m), 1.07 (3H, d, *J* = 6.8 Hz), 1.05 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.6 (C), 175.3 (C), 141.8 (C), 141.7 (C), 138.5 (C), 130.7 (CH), 130.4 (CH), 129.2 (CH), 128.8 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 127.0 (CH), 71.7 (CH), 42.1 (CH), 40.8 (CH_2), 30.9 (CH), 30.1 (CH), 19.0 (CH_3), 17.7 (CH_3), 12.1 (CH_3).

*(S)-N-[(R)-2-(4-Benzhydrylphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (**10a**).* Thick yellow oil. R_f 0.50 (60:40 CH_2Cl_2/hexanes). $[\alpha]_D^{20}$ +112.0 (*c* 1.00, $CHCl_3$). IR (ATR) ν 2958, 1689, 1591, 1350, 1245, 1147, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32−7.03 (14H, m), 5.95 (1H, q, *J* = 6.9 Hz), 5.51 (1H, s), 5.19−5.09 (1H, m), 3.38 (1H, dd, *J* = 11.4, 8.7 Hz), 2.97 (1H, dd, *J* = 11.4, 3.5 Hz), 2.07−1.96 (1H, m), 1.50 (3H, d, *J* = 6.9 Hz), 0.83 (3H, d, *J* = 7.0 Hz), 0.63 (3H, d, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.4 (C), 176.9 (C), 143.8 (C), 142.9 (C), 137.9 (C), 129.6 (CH), 129.4 (CH), 129.3 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.3 (CH), 126.3 (CH), 72.2 (CH), 56.5 (CH), 44.6 (CH), 30.0 (CH_2), 28.9 (CH), 19.3 (CH_3), 19.0 (CH_3), 16.0 (CH_3). HRMS (+ESI): m/z calcd for $C_{28}H_{30}NOS_2$ $[M + H]^+$ 460.1763; found 460.1751.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00657.

Copies of ^1H and ^{13}C NMR for unreported *N*-acyl thiazoldinethiones **1f** and **1i** and compounds **2**−**10** (PDF)

X-ray data for **2d** (CIF)

X-ray data for **2h** (CIF)

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Notes

The authors declare no competing financial interest.

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