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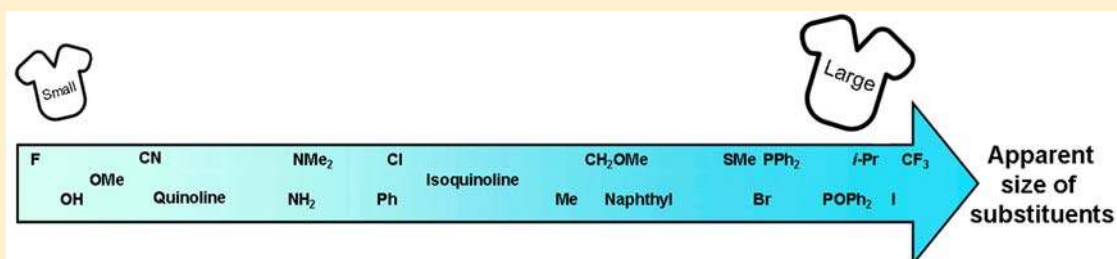
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Steric Scale of Common Substituents from Rotational Barriers of *N*-(*o*-Substituted aryl)thiazoline-2-thione Atropisomers

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ABSTRACT: A steric scale of 20 recurrent groups was established from comparison of rotational barriers on *N*-(*o*-substituted aryl)thiazoline-2-thione atropisomers. The resulting energy of activation $\Delta G_{\text{rot}}^{\ddagger}$ reflects the spatial requirement of the ortho substituent borne by the aryl moiety, electronic aspects and external parameters (temperature and solvent) generating negligible contributions. Concerning divergent rankings reported in the literature, the great sensitivity of this model allowed us to show unambiguously that a methyl appears bigger than a chlorine and gave the following order in size: CN > OMe > OH. For the very bulky CF₃ and *i*Pr groups, constraints in the ground state decreased the expected $\Delta G_{\text{rot}}^{\ddagger}$ values resulting in a minimization of their apparent sizes.

INTRODUCTION

Steric effects arise from the fact that atoms of a molecule are located in a particular manner in the space. The reactivity and the conformation of a structure are directly affected by the steric size and the proximity of molecular groups which constitute it. Consequently, understanding steric effects represents a significant interest in several areas of chemistry such as quantitative structure–activity relationship (QSAR)¹ and the design of drugs,² molecular machines³ and catalysts.⁴ It is also a major aspect to consider in medicinal chemistry to rationalize biological⁵ or enzymatic activities⁶ and in synthesis to explain reactivity⁷ and stereochemistry⁸ or to propose mechanisms.⁹ Furthermore, careful attention must be paid to steric parameters during investigations on nanomaterials¹⁰ and in dynamic stereochemistry.¹¹

Therefore, ranking molecular fragments according to their apparent size represents a crucial point of interest. Measurements of steric bulk such as the Taft E_s values were first derived from kinetic data¹² and considerable efforts were devoted to the separation of electronic from purely steric contributions in these models.¹³ In order to minimize the electronic contribution, a steric scale of substituents can be established from the determination and comparison of rotational barriers on a scaffold in which these molecular fragments hinder directly the rotation about an axis. This approach to the problem appears attractive and elegant, and the two landmark studies concerning this issue have been carried out by Sternhell et al.¹⁴ and Mazzanti, Ruzziconi, Schlosser et al.¹⁵ These works are based on a similar concept: the determination of rotational

barrier about a C_{aryl}–C_{aryl} bond on conformers by dynamic nuclear magnetic resonance (Figure 1). Note that these two scales do not always agree with respect to the ranking of some recurrent groups in chemistry, for instance, the order between the apparent sizes of Me versus Cl or in the triad OH/OMe/CN.

We report herein the first steric scale developed on thermal racemization of atropisomers¹⁶ of an *N*-arylthiazoline-2-thione template **1** (Figure 1). These atropisomers were separable by HPLC on chiral support, and the rotational barriers were determined without the requirement of a probe on the structure. These compounds have been widely employed in organic synthesis as precursors of dithiadiazafulvalenes,¹⁷ heterocycles,¹⁸ sulfur derivatives,¹⁹ and *N*-heterocyclic carbenes.²⁰ Interestingly, *N*-(*o*-substituted aryl)thiazoline-2-thiones were considered as model structures to investigate the chiral recognition mechanism of commercial chiral stationary phases²¹ and to evaluate a chiral solvating agent for NMR determination of enantiomeric composition.²² Indeed, *N*-(*o*-substituted aryl)thiazoline-2-thiones are composed of a heterocycle and an aryl group that are situated in two nearly perpendicular planes due to the restricted rotation about the N–C_{aryl} bond, giving rise to two atropisomers.²³ The resulting barrier to rotation is directly connected to the substituent borne in ortho position of the aryl group. Furthermore, the heterocyclic moiety of the *N*-aryl-thiazoline-2-thione scaffold

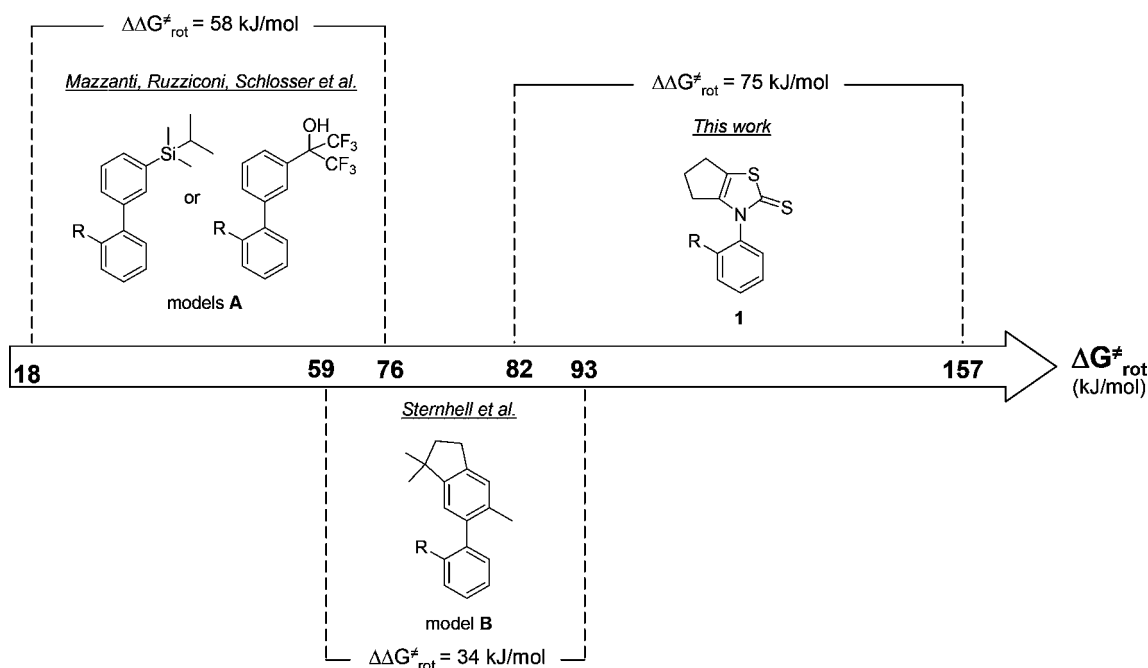


Figure 1. Range of rotational barriers for the scaffolds used to establish a steric scale.

exhibits a methylene and a thione group in the blocking positions leading to greater $\Delta G_{\text{rot}}^{\ddagger}$ values compared with models A (two hydrogens in the corresponding blocking positions) and model B (a methyl and a hydrogen atom in the corresponding blocking positions) as depicted in Figure 1. Besides all these aspects which are particularly suitable to achieve our goal, a huge molecular diversity can be introduced in ortho position since *N*-(*o*-substituted aryl)thiazoline-2-thiones were obtained starting from commercial anilines via a straightforward and efficient sequence.²³

RESULTS AND DISCUSSION

Validation of the *N*-Arylthiazoline-2-thione Template 1 To Establish a Steric Scale. Preliminary investigations were directed toward thiazoline-2-thiones **1a–d** bearing a halogen atom in the ortho position of the rotating aryl group. These reference series allowed an accurate evaluation of the potential of our framework as a large spectrum of size is covered from the very small fluorine atom to one of the bigger substituents, iodine.




The desired *N*-(*o*-substituted aryl)thiazoline-2-thiones were synthesized using a procedure that we have previously reported:²³ treatment of commercial aniline with carbon disulfide to generate the dithiocarbamate salt, which was allowed to react with 2-chlorocyclopentanone to furnish **1**. Enantiomers were obtained by preparative HPLC on chiral support on the so-called (*S,S*) Whelk-O1 column. This commercial chiral stationary phase is particularly suitable for the separation of atropisomers of *N*-(*o*-substituted aryl)thiazoline-2-thiones which present both a π -basic site and a hydrogen-bond acceptor site near a stereogenic element.^{21c} Each rotational barrier was then determined by kinetic study of the thermal racemization of atropisomers at a given temperature. To fix a constant temperature and avoid fluctuation due to heating apparatus, the kinetic studies were carried out in a refluxing solvent. The solvent was thus selected depending on its boiling point in order to follow conveniently the

racemisation process over at least one-half-life. The resulting Gibbs free energy of activation $\Delta G_{\text{rot}}^{\ddagger}$ was finally obtained from the Eyring equation (Table 1).²⁴

The rotational barriers for the set of halogenated derivatives were easily determined although a plateau shape was observed on the chromatogram for compound **1a** substituted with a fluorine atom. In this case, the barrier to rotation was estimated at 82.5 kJ/mol from the chromatogram profile according to the Trapp and Schurig equation.²⁵ This value was very close to the lower limit reachable by HPLC on chiral support without calling for cryochromatography.²⁶ For the iodine derivative **1d**, the barrier to rotation was measured as 155.5 kJ/mol. Moreover, a crystal of a pure enantiomer of **1b** was grown for absolute configuration determination by X-ray diffraction²⁴ (Figure 2) and the first eluted enantiomer on the (*S,S*) Whelk-O1 column was the (*S_n*)-enantiomer as expected.^{21c} A crucial information can be gleaned from this the solid state structure: the angle between the nitrogen of the thiazoline ring and the methylene of five-membered ring was measured as 131°. This value is particularly higher than 120–121° found for the *N*-arylthiazoline-2-thione analogues bearing a methyl in position 4 of the thiazoline ring instead of the methylene group.^{23,19} This structural difference in one blocking position produces a significant change in the resulting energy of activation $\Delta G_{\text{rot}}^{\ddagger}$ making the rotation around the pivotal bond easier for thiazoline-2-thiones **1** compared to the 4-methyl analogues.²³ These remarks suggest that the promising scaffold **1** will provide rotational barriers in a very suitable range from small to bulky substituents.

To fully validate the choice of the framework **1**, the $\Delta G_{\text{rot}}^{\ddagger}$ values of the halogenated thiazoline-2-thiones **1a–d** were plotted versus the corresponding results reported for model B (Figure 3).²⁷ This revealed a perfect alignment with a correlation coefficient of 0.9998 and a greater sensitivity to steric effect in the thiazoline-2-thione scaffold (slope = 2.72). The comparative study with the halogen atoms was enriched by the methyl group which presents a different electronic behavior. The rotational barrier of the thiazoline-2-thione **1e** with a

Table 1. Rotational Barriers of *N*-(*o*-Substituted aryl)thiazoline-2-thiones **1 and Corresponding Values from Models A and B**

R		$\Delta G_{\text{rot}}^{\ddagger}$ for 1 in kJ/mol (solvent; temperature)	$\Delta G_{\text{rot}}^{\ddagger}$ for A (kJ/mol)	$\Delta G_{\text{rot}}^{\ddagger}$ for B ^b (kJ/mol)
F	1a	82.5 ^a (hexane/ethanol 7/3; 5°C)	18.4	59.6
Cl	1b	133.3 (chlorobenzene; 131°C)	32.2	78.5
Br	1c	145.5 (1,2-dichlorobenzene; 182°C)	36.4	82.9
I	1d	155.5 (1,2-dichlorobenzene; 182°C)	41.8	86.3
Me	1e	140.9 (1,2-dichlorobenzene; 182°C)	30.9	80.9
<i>i</i> Pr	1f	153.5 (1,2-dichlorobenzene; 182°C)	46.4	93.0
Ph	1g	132.7 (1-butanol; 118°C)	31.4	73.5
CH ₂ OMe	1h	141.2 (1,2-dichlorobenzene; 179°C)	-	-
CN	1i	110.5 (chloroform; 61°C)	24.7	66.0
CF ₃	1j	156.8 (1,2-dichlorobenzene; 182°C)	43.9	92.0
NH ₂	1k	124.9 (ethanol; 79°C)	33.9	80.6
NMe ₂	1l	125.6 (ethanol; 78°C)	28.8	73.1
OH	1m	96.2 ^a (hexane/ethanol 8/2; 40°C)	22.6	67.5
OMe	1n	104.7 (chloroform; 40°C)	23.4	66.9
PPh ₂	1o	147.3 (1,2-dichlorobenzene; 179°C)	39.3	-
POPh ₂	1p	152.8 (1,2-dichlorobenzene; 179°C)	42.6	-
SMe	1q	145.3 (1,2-dichlorobenzene; 182°C)	35.9	81.7
	1r	142.6 (chlorobenzene ; 132°C)	-	-
	1s	136.2 (chlorobenzene ; 132°C)	-	-
	1t	111.4 (ethanol ; 78°C)	-	-

^aObtained by dynamic chiral HPLC (online plateau treatment). ^b $\Delta G_{\text{rot}}^{\ddagger}$ at 340 K calculated using $\Delta S_{\text{av}}^{\ddagger}$, the average entropy activation for the whole series

methyl group was estimated as 140.9 kJ/mol. This value was plotted against the $\Delta G_{\text{rot}}^{\ddagger}$ of the methyl derivative in model B and the resulting point was exactly on the halogens trendline (Figure 3). These findings highlighted that rotational barriers in series **1** were predominantly influenced by steric contributions, and that comparison of $\Delta G_{\text{rot}}^{\ddagger}$ values with model B was relevant whatever the chemical identity of the studied substituent.

Similar plotting was carried out with models A, but herein the correlation was not as nice as in the previous case (Figure

4). It is, however, noticeable that in this scale the determination of the apparent size of the fluorine atom was performed by ¹⁹F NMR at very low temperature using a different probe compared to the other substituents. Unfortunately, the two probes did not generate an identical result for a same substituent. For instance, for the evaluation of the apparent size of the bromine, the initial probe furnished a rotational barrier of 34.7 kJ/mol^{15a} against 36.4 kJ/mol^{15b} with the probe used for the determination of the size of the fluorine, a difference which must be considered as explained thereafter. Adding results for the methyl group on

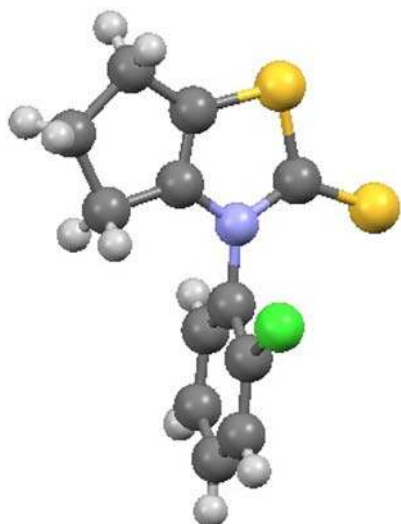


Figure 2. X-ray structure of a pure enantiomer of (*S*_a)-1b.

Figure 4 revealed another disagreement between steric scales from models A with model 1, and thus also with model B. The apparent size of Me in the scales from models A, B and 1, as well as its ranking versus the chlorine atom will be discussed in detail later in this paper.

Besides these two well-established scales, Dogan et al.²⁸ and Orelli et al.²⁹ have described the effect of the nature of halogen located in ortho position of a rotating aryl group on *N*-*C*_{aryl} and *C*-*C*_{aryl} atropisomeric scaffolds respectively (Figure 5). These studies afforded an additional benefit to examine preliminarily the halogenated series. Here again, a very good agreement was observed in both cases for the $\Delta G^{\ddagger}_{\text{rot}}$ values, as well as a higher sensitivity for the scaffold 1 (see the corresponding slopes in Figure 5).

Considering these outcomes, we can notice that the rotational barriers in the halogenated series 1a–d correlates accurately with corresponding values from other templates exhibiting different structural and functional environment. We can assume that this indicates that the barriers to rotation measured on thiazoline-2-thiones 1 clearly reflect the apparent size of the molecular fragment borne in ortho position of the rotating aryl group. In addition, when comparing the $\Delta G^{\ddagger}_{\text{rot}}$ values of the halogenated thiazoline-2-thiones 1a–d to their corresponding derivatives in the four other models, the slopes were in each case larger than 1 (Figures 3–5). This emphasizes a major characteristic of model 1 which exhibited a higher sensitivity to steric strain.

At this stage, particular attention was devoted to demonstrate the accuracy of the methodology employed and to confirm that the resulting scale would be a proper view of the apparent size of substituents. To achieve these aims, the initial series was extended by two new substituents in ortho position of the aryl moiety: NMe₂³⁰ and OMe (derivatives 1l and 1n, respectively).

The repeatability of the measurement of barriers to rotation was first evaluated. The determination of the rotational barrier of compound 1c was performed five times exactly in the same conditions (in 1,2-dichlorobenzene at 179 °C). The Gibbs free energies of activation of this set were included within the range 145.3–145.4 kJ/mol showing a highly repeatable protocol.²⁴

The barriers to rotation can be influenced by the solvent³¹ and kinetic experiments were carried out in different solvents at the same temperature to reveal a possible effect on our scaffold. The rotational barrier of 1l at 78 °C was measured at 125.9 kJ/mol in acetonitrile versus 125.6 kJ/mol in ethanol. For compound 1n, we obtained 104.7 kJ/mol in chloroform compared to 105.3 kJ/mol in ethanol, both at 40 °C. The nature of the solvent (polar/apolar and protic/aprotic)³² has thereby exerted a negligible impact on the rotational barrier, taking into account the width of the covered range in the *N*-(*o*-substituted aryl)thiazoline-2-thione series 1 (from 82.5 to 156.8 kJ/mol; Table 1).

Apart from its nature, the solvent used also imposes the temperature for the kinetic experiments because it is preferable to heat at reflux as explained previously. Nevertheless, to investigate temperature effects, the Gibbs free energies of activation of five *N*-(*o*-substituted aryl)thiazoline-2-thiones were carefully evaluated on a wide range of temperature and in the same solvent for each compound reported in Table 2. Eyring plots allowed access to the activation enthalpy ΔH^{\ddagger} and entropy ΔS^{\ddagger} contributions.³³ The corresponding ΔS^{\ddagger} values were small and negative, indicating a highly ordered transition state which is typical for atropisomerizations,³⁴ and they were also consistent with related structures.^{35,31d} Furthermore, compared to parameters from model B (ΔS^{\ddagger} average = -79 J·K⁻¹·mol⁻¹), the activation entropies in the *N*-(*o*-substituted aryl)thiazoline-2-thione series were smaller, pointing out an enantiomerization with low temperature dependence. For instance, thiazoline-2-thione 1c exhibited a ΔS^{\ddagger} of -21 J·K⁻¹·mol⁻¹, which represents a variation of merely 1 kJ/mol for the $\Delta G^{\ddagger}_{\text{rot}}$ over 50 °C. Above all, the activation entropies of the tested thiazoline-2-thiones were in a narrow range (from -21 to -40 J·K⁻¹·mol⁻¹) showing a homogeneous series regarding the temperature dependence. The conditions employed during the kinetics (solvent and temperature) did not significantly influence the rotational barriers in the *N*-(*o*-

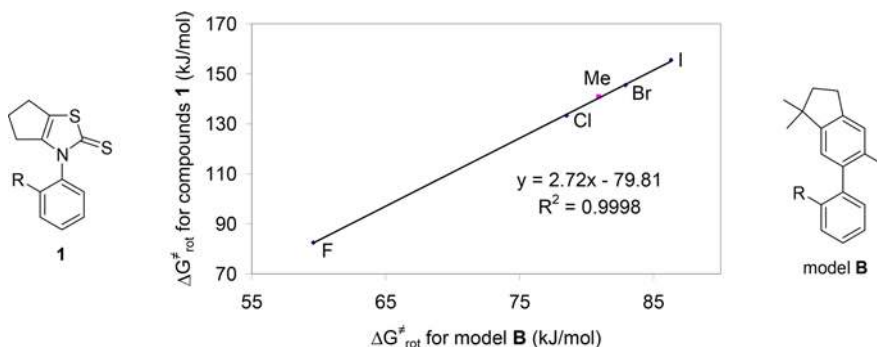


Figure 3. Halogenated series 1a–d and methyl derivative 1e vs model B.

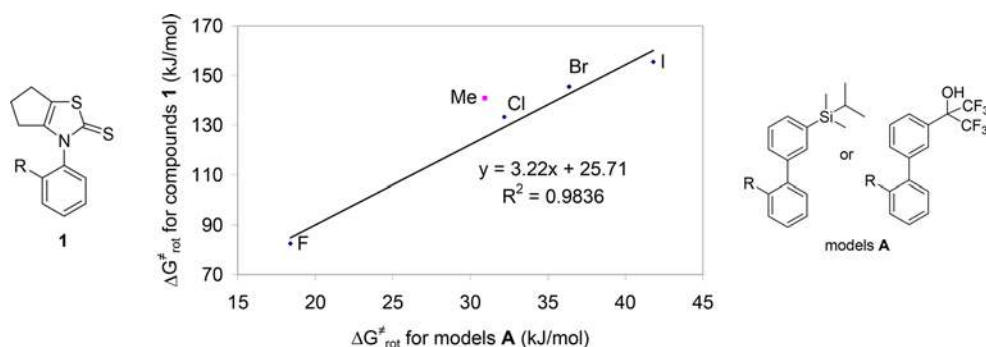


Figure 4. Halogenated series 1a–d and methyl derivative 1e vs models A.

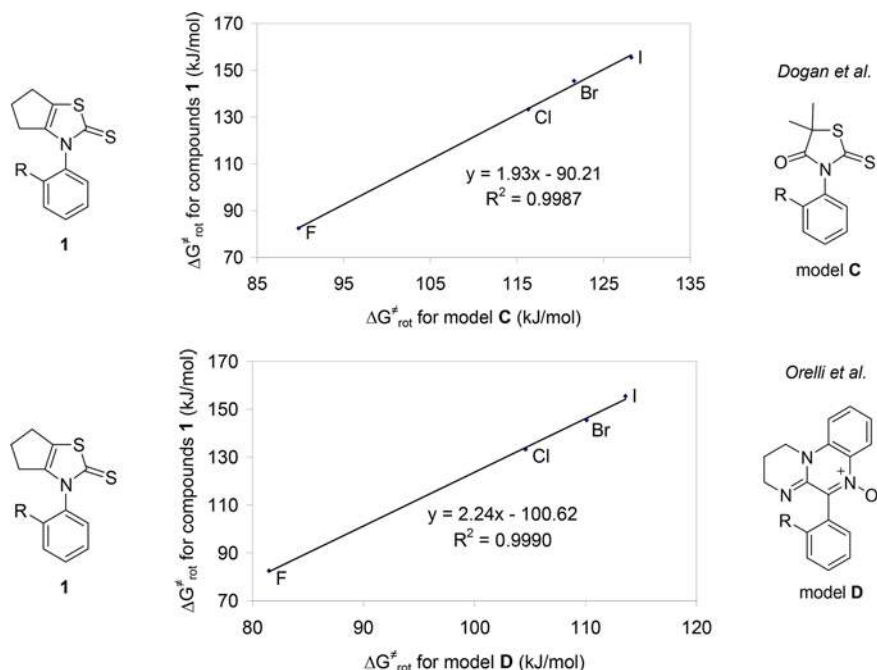


Figure 5. Halogenated series 1a–d vs model C and model D.

Table 2. Enthalpy and Entropy Parameters

	R	ΔH^\ddagger (kJ/mol)	ΔS^\ddagger (J·K ⁻¹ ·mol ⁻¹)	temp range (°C)	solvent
1b	Cl	117.9	-36	115–161	1,2-dichlorobenzene
1c	Br	135.8	-21	123–182	1,2-dichlorobenzene
1e	Me	125.6	-34	119–182	1,2-dichlorobenzene
1l	NMe ₂	108.7	-40	78–132	chlorobenzene
1n	OMe	92.6	-40	25–78	ethanol

substituted aryl)thiazoline-2-thione series considering the magnitude of the $\Delta G^\ddagger_{\text{rot}}$ range.

Finally, the contribution of electronic aspects on rotational barriers has been reported in the literature.^{36,31c} Such effects can arise in the planar transition state, modifying the electron density of the pivotal bond. To explore this point, two series of *N*-(*o*-substituted aryl)thiazoline-2-thiones bearing an additional substituent in para position were prepared. The para position was chosen to maximize the electronic contribution of the substituent and to minimize buttressing effect. The ortho substituent was either a methyl group or a chlorine atom, whereas the para substituents could be electron-withdrawing (F) or electron-donating (OMe, Me) groups (Table 3). The rotational barriers were determined in the same refluxing solvent and disclosed that these modifications involved a slight

Table 3. Rotational Barriers of *N*-(*o,p*-Disubstituted aryl)thiazoline-2-thiones

	R ¹	Rotational barrier (kJ/mol)	T (°C)	Solvent
2a	Me	132.9	131	chlorobenzene
	F	133.4	131	chlorobenzene
2c	OMe	140.7	179	1,2-dichlorobenzene
2d	F	140.8	179	1,2-dichlorobenzene

variation on the $\Delta G_{\text{rot}}^{\ddagger}$ values compared to the corresponding monosubstituted derivatives **1b** ($\Delta G_{\text{rot}}^{\ddagger} = 133.3$ kJ/mol to be compared to barriers for **2a,b**) or **1e** ($\Delta G_{\text{rot}}^{\ddagger} = 140.9$ kJ/mol to be compared to barriers for **2c,d**). These results validated the thiazoline-2-thione framework to accomplish the intended purpose showing that the rotational barriers in these series were very mainly governed by steric hindrance of the ortho substituent. Evaluation and comparison of the apparent size of molecular fragments make sense through these Gibbs free energies of activation.

Extension to Other Substituents and Comparison with Previous Models. We then concentrated our efforts on the synthesis of a focused library of *N*-(*o*-substituted aryl)-thiazoline-2-thiones with the aim of determining the effective size of substituents commonly used in chemistry. Indeed, substituents installed in ortho position of the rotating aryl group are diversified with regards to their bulkiness and chemical nature. We also focused on functional groups often found such as the trifluoromethyl group in medicinal chemistry or PPh_2 in catalysis.

As previously mentioned, *N*-(*o*-substituted aryl)thiazoline-2-thiones were obtained from a protocol that we have already described. However, in a few cases, this methodology was unsuccessful because of poor reactivity of the starting aniline due to low nucleophilicity or/and steric hindrance. To tackle this issue, alternative pathways were employed and specific details are given in [Supporting Information](#). The demethylation of the methoxy compound **1n** by BBr_3 afforded **1m**.^{23a} **1i**, **1o**, and **1p** (CN, PPh_2 , and POPh_2 in ortho position respectively) were generated from a treatment on the *o*-bromothiazoline-2-thione **1c** with *n*BuLi.³⁷ Finally, the CF_3 derivative **1j** was isolated using a modification in the original method.³⁸ All of the prepared racemates were then separated into enantiomers by preparative HPLC using the (S,S) Whelk-O1 column.

The ΔG^{\ddagger} values for rotational barriers of *N*-arylthiazoline-2-thiones diversely substituted in the *o*-aryl position are gathered in the [Table 1](#). Interesting remarks into the apparent size of the corresponding functional groups can be gleaned from a careful examination of these results. A well-established phenomenon was confirmed: the CF_3 motif ($\Delta G_{\text{rot}}^{\ddagger} = 156.8$ kJ/mol) is much bigger than a methyl ($\Delta G_{\text{rot}}^{\ddagger} = 140.9$ kJ/mol) and can be considered as an isostere of *i*Pr ($\Delta G_{\text{rot}}^{\ddagger} = 153.5$ kJ/mol). In terms of steric demand, the diphenylphosphine fragment ($\Delta G_{\text{rot}}^{\ddagger} = 147.3$ kJ/mol) appears similar to a SMe substituent ($\Delta G_{\text{rot}}^{\ddagger} = 145.3$ kJ/mol) or a bromine atom ($\Delta G_{\text{rot}}^{\ddagger} = 145.5$ kJ/mol) whereas its oxygenated analogue POPh_2 ($\Delta G_{\text{rot}}^{\ddagger} = 152.8$ kJ/mol) is bigger, with a spatial requirement identical to an isopropyl group. Moreover, thiazoline-2-thiones bearing a NH_2 group **1k** or a NMe_2 group **1l** exhibited very close $\Delta G_{\text{rot}}^{\ddagger}$ values (124.9 kJ/mol vs 125.6 kJ/mol). This interesting observation comes presumably from the fact that the stabilizing conjugation at the ground state of the NH_2 lone pair is lost at the transition state, increasing the required energy to rotate as already supported by computational calculations on models **A**.^{15a} Moreover, the barriers to rotation for the CH_3 and CH_2OMe derivatives were measured as 140.9 and 141.2 kJ/mol respectively, meaning that the methoxy group is oriented to minimize the steric hindrance and has therefore a small impact on the rotational barrier. Compared to these results, compound **1r** with a naphthyl group displayed a slightly higher $\Delta G_{\text{rot}}^{\ddagger}$ value (142.6 kJ/mol) which can be attributed to the steric interaction of the $\text{C}(8)_{\text{aryl}}\text{-H}$ bond in the transition state. The fact that naphthyl appears bigger than methyl is in accordance

with studies reported by Mannschrek³⁹ and Dogan.⁴⁰ In addition, the following order emerges by comparing rotational barriers of **1r**, **1s** and **1t**: naphthyl ($\Delta G_{\text{rot}}^{\ddagger} = 142.6$ kJ/mol) > 5-isoquinoline ($\Delta G_{\text{rot}}^{\ddagger} = 136.2$ kJ/mol) > 8-quinoline ($\Delta G_{\text{rot}}^{\ddagger} = 111.4$ kJ/mol), showing the smaller steric demand of a nitrogen lone pair compared with a C–H bond. It is interesting to note that a different ranking has been described for this set of three motifs ([Figure 6](#)).⁴¹ However, for this succinimide-based framework, a lone pair/lone pair repulsion takes place between the 8-quinoline nitrogen and the imide oxygen in the transition state.

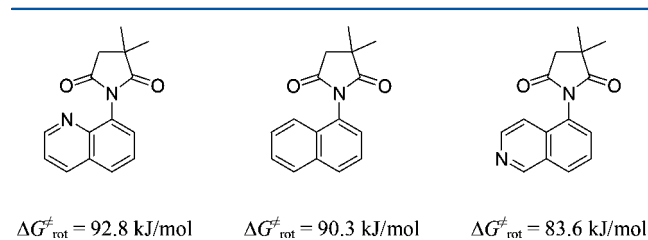


Figure 6. Rotational barriers of 8-quinoline/naphthyl/5-isoquinoline succinimides.

Steric scales from models **A** and **B** do not always match despite the fact that both were obtained from biaryl scaffolds ([Figure 7](#)),²⁷ and an important contribution of our work can be found in these divergent cases. This is particularly true for two sets of values including very popular molecular fragments in chemistry (surrounded areas in [Figure 7](#)). The first discordance concerns the OH/OMe/CN series where two opposite rankings are described. For model **B**, the order in size is OH > OMe > CN instead of CN > OMe > OH for models **A**.⁴² These latter findings are corroborated by our scale since the methoxy motif ($\Delta G_{\text{rot}}^{\ddagger} = 104.7$ kJ/mol) is comprised between the bigger cyano ($\Delta G_{\text{rot}}^{\ddagger} = 110.5$ kJ/mol) and the smaller OH ($\Delta G_{\text{rot}}^{\ddagger} = 96.2$ kJ/mol). Another disagreement between steric scales from models **A** and **B** consists in the ranking of methyl, chloro and phenyl substituents.⁴³ Using the *N*-arylthiazoline-2-thione model, the rotational barrier for the methyl derivative **1e** was estimated at 140.9 kJ/mol versus 133.3 kJ/mol for the chloro derivative **1b**. The same holds true in the steric scale from template **B**, and this behavior is also consistent with the van der Waals radii of these two fragments from X-ray crystallographic measurements.⁴⁴ Surprisingly, the chlorine is described bigger than the methyl in models **A**. This reverse order has been previously reported but it was always attributed to an electrostatic interaction in the transition state between the chlorine atom and a heteroatom, this repulsion involving an energy penalty for the chloro derivative.^{29,35b,39,40a,45} According to the above discussion, the ranking Me > Cl observed with model **I** strongly suggests that the rotation about the pivotal N-C_{aryl} bond takes place through the pathway leading the *N*-aryl ortho substituent close to the thiazoline methylene group and not to the thione sulfur atom in the planar transition state. Furthermore, whereas the sizes of Me and Ph are similar in models **A**, the methyl group ($\Delta G_{\text{rot}}^{\ddagger} = 140.9$ kJ/mol) is significantly larger than the phenyl group ($\Delta G_{\text{rot}}^{\ddagger} = 132.7$ kJ/mol) in our case as well as in the scale from **B**, indicating a rotation about the $\text{C}_{\text{aryl}}\text{-C}_{\text{aryl}}$ bond to minimize steric interactions in the transition state.

The scales from models **A** and **B** are based on a biaryl scaffold, and these two divergences in the ranking are quite unexpected since a similar behavior and a uniform sensitivity to

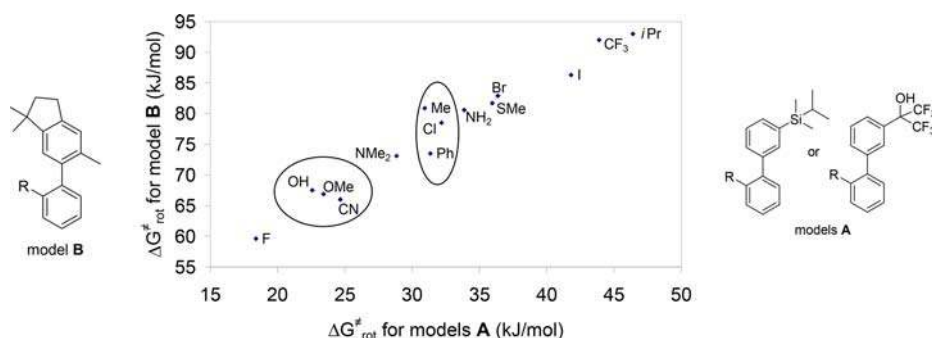


Figure 7. Model B vs models A.

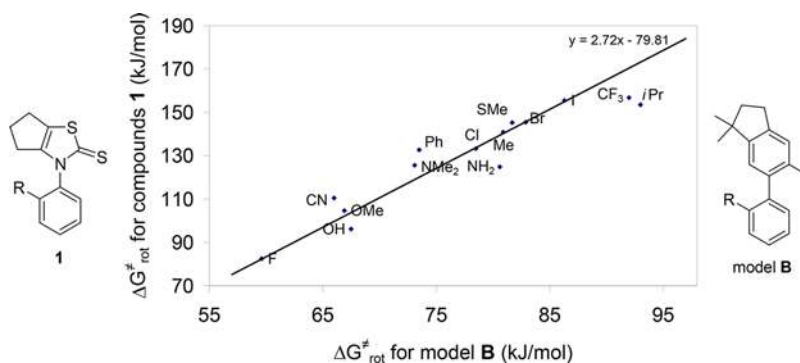


Figure 8. Model 1 vs model B.

peripheral effects could be anticipated. The origin of these discordances could be the consequence of the very narrow range of $\Delta G_{\text{rot}}^{\ddagger}$ values in these two models. To illustrate this point, the $\Delta\Delta G_{\text{rot}}^{\ddagger}$ between fluorine and iodine derivatives accounts for 73.0 kJ/mol in the *N*-(*o*-substituted aryl)-thiazoline-2-thione series, compared with 23.4 kJ/mol for models A and 26.7 kJ/mol for model B. Steric effects must obviously represent the very dominant contribution on the rotational barriers but it is also highly suitable that the enantiomerization process exhibits significant energy variation in order to minimize the influence of external parameters. About the controversial Cl/Me ranking, the template 1 furnishes a $\Delta\Delta G_{\text{rot}}^{\ddagger}$ of 7.6 kJ/mol which is large enough to overlook solvent, temperature and electronic effects. The corresponding $\Delta\Delta G_{\text{rot}}^{\ddagger}$ represent 1.3 and 2.4 kJ/mol for frameworks A and B respectively. A similar observation can be noticed for the triad OH/OMe/CN: the corresponding $\Delta G_{\text{rot}}^{\ddagger}$ values for rotational barriers in 1 are scattered on 14.3 kJ/mol against 2.1 kJ/mol in the scale from A and 1.5 kJ/mol in the scale from B. Small gaps between groups involve that external parameters to the size might impact the ranking, leading in some cases to a reverse order of molecular fragments. This kind of problem is strongly limited in the *N*-(*o*-substituted aryl)thiazoline-2-thione series 1 thanks to the great sensitivity of this model to the size of the *o*-aryl substituent.

Taking into account the conclusions mentioned for model B during preliminary investigations on the halogenated series and methyl group, we carried out an extended comparative study on the 14 substituents found in both models B and 1 (Figure 8). The following discussion was directed using the halogens trendline ($2.72x - 79.81$) as a reference. The two scales are generally in good agreement for substituents exhibiting small to large steric demand. Some small disagreements can be detected for the apparent sizes of OH and NH₂ which are minimized in

the scale from model 1 contrary to the cyano and phenyl which are depicted above the trendline. In these last cases, electronic interactions between the polar heterocycle and the *p*-orbitals of multiple bonds could influence the $\Delta G_{\text{rot}}^{\ddagger}$ values of the related compounds. However, for very bulky groups, the correlations clearly show that model 1 leads to rotational barriers lower than the expected values which would be obtained by following the trend observed with model B. This behavior is limited to the biggest substituents i.e. the *isopropyl* and the trifluoromethyl, since even for the bulky iodine atom, a very good matching is noticed (see Figure 3 and related paragraph). This intriguing phenomenon can be attributed to the large steric requirement of *iPr* and CF₃ which increase the energy of the ground state. Thus, the corresponding rotational barriers are lower taking in mind that the measured $\Delta G_{\text{rot}}^{\ddagger}$ values represent the energetic gap between the constraints in the ground state and in the transition state. This limitation of the scale established from *N*-arylthiazoline-2-thiones 1 is a counterpart of the advantage to access high $\Delta G_{\text{rot}}^{\ddagger}$ values as reported previously. Consequently, the size of these very bulky substituents appears smaller than expected. For compounds 1f and 1j, we can propose theoretical $\Delta G_{\text{rot}}^{\ddagger}$ values which would be reached without constraints in the ground state. Using the equation of the halogens trendline and the $\Delta G_{\text{rot}}^{\ddagger}$ values of related compounds from B, the rotational barriers should be measured as 170.4 kJ/mol for the *isopropyl* derivative 1f and 173.2 kJ/mol for the trifluoromethyl derivative 1j. The experimental barriers to rotation are lower by 19.7 kJ/mol for 1f and 13.6 kJ/mol for 1j. These differences reveal what we may consider as a limitation of our model: the influence of ground state strain in the case of very large substituents. This point has to be considered when discussing rotational barriers on a particular framework, as well as in the choice of a steric scale to address specific question.

To complete this study, results obtained from model 1 were plotted to standard steric parameters (Table 4 and Figure 9). E_s

Table 4. Taft, Charton, and Sterimol Parameters

	E_s (Taft parameter)	ν (Charton parameter)	B_1 (Sterimol parameter)	L (Sterimol parameter)
F		0.27	1.35	2.65
Cl	0.09	0.55	1.8	3.52
Br	-0.06	0.65	1.95	3.82
I	-0.29	0.78	2.15	4.23
CH ₃	0	0.52	1.52	2.87
<i>i</i> Pr	-0.47	0.76	1.9	4.11
CF ₃	-1.16	0.9	1.99	3.3
OH		0.32	1.35	2.74
OMe	1.11	0.36	1.35	3.98
SMe		0.64	1.7	4.3
NH ₂		0.35	1.35	2.78
NMe ₂		0.43	1.35	3.53
CN		0.4	1.6	4.23
Ph			1.71	6.28
CH ₂ OMe		0.63		

Taft parameters were developed experimentally from kinetic data of acidic catalyzed hydrolysis of esters.^{12,13b} Thus, this scale is particularly suitable for large alkyl groups but limited for other functional groups, and only seven substituents are found both in Taft scale and ranking from 1. The correlation is moderate for plots of $\Delta G_{\text{rot}}^\ddagger$ values of 1 versus E_s Taft parameters (Figure 9a) but confirms the already quoted tendency of model 1 to underestimate the size of the very bulky CF₃ motif. The same holds true when comparing the rotational barriers of *N*-aryl-thiazoline-2-thiones 1 to the ν Charton steric parameters calculated from the van der Waals radii (Figure 9b).⁴⁶ In addition, according to Charton, NH₂ appears clearly smaller than NMe₂ contrary to the results found with rotating aryl models A, B, and 1. This fully supports the hypothesis mentioned previously, namely a stabilizing conjugation at the ground state of the NH₂ lone pair with the aromatic ring increasing the corresponding $\Delta G_{\text{rot}}^\ddagger$ values in the case of models A, B and 1 (see related paragraph). Finally, the Sterimol parameters represent a set of computational parameters often used in QSAR and divide in subparameters among which the most significant are B_1 (describing the minimum width of the substituent) and L (a length parameter).⁴⁷ Plottings of each of these two parameters versus model 1 show a poor correlation, particularly with L parameter (Figure 9c,d). However, lecture of this type of plotting has to be handled with high care since such comparison is carried out with a single Sterimol parameter which depicted a specific dimensional property (involving for instance an identical B_1 parameter for five different substituents F, OH, OMe, NH₂, and NMe₂) and not an overall evaluation of the steric size.

In conclusion, rotational barriers on *N*-(*o*-substituted aryl)-thiazoline-2-thiones reflects accurately the spatial requirement of the ortho molecular fragment borne by the rotating aryl group. This allowed the establishment of a new steric scale for groups commonly used in chemistry. The range of the $\Delta G_{\text{rot}}^\ddagger$ values is very broad and thus substituents with close sizes produce significantly different $\Delta G_{\text{rot}}^\ddagger$. Therefore, the ranking according to the $\Delta G_{\text{rot}}^\ddagger$ values is not perturbed by the negligible contributions of the electronic and experimental parameters. Thereby, when discordant results were emerging

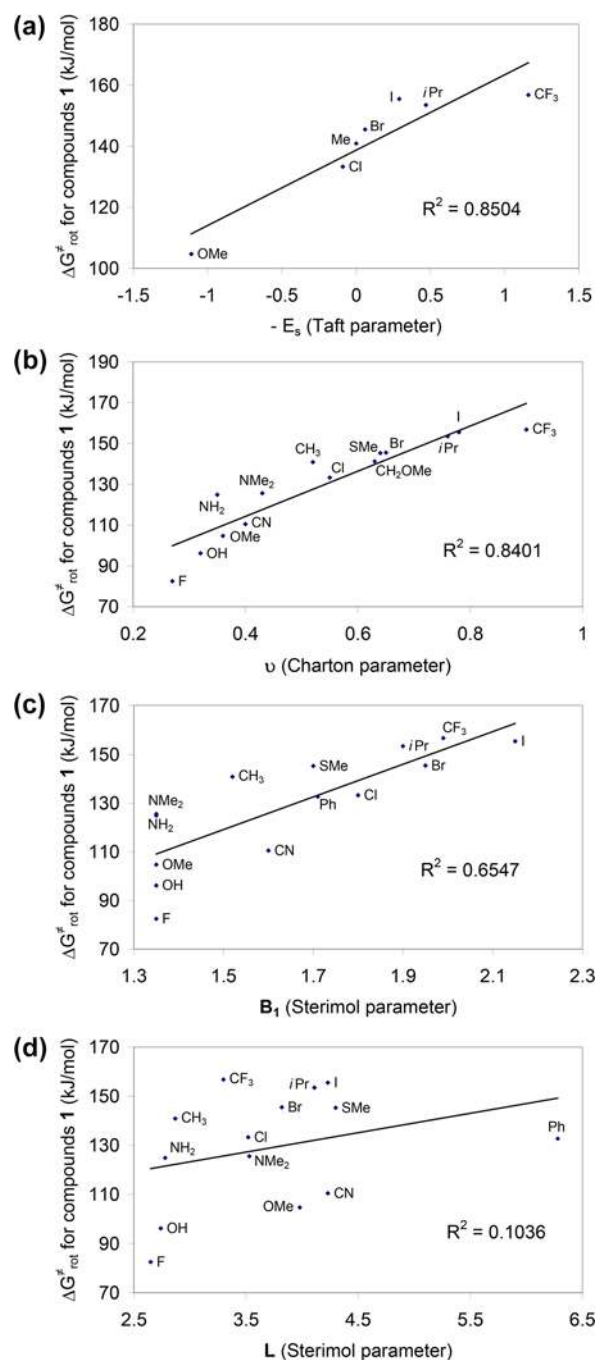


Figure 9. Model 1 vs standard steric parameters.

from previously reported studies, our scale shows that a methyl appears bigger than a chlorine atom and gives moreover the following order in size CN > OMe > OH. In return, this great sensitivity of framework 1 to steric modification of the ortho-aryl substituent lead to a limitation of the model for very bulky substituents (CF₃ and *i*Pr) whose apparent sizes were significantly reduced due to ground state strain.

EXPERIMENTAL SECTION

General Information. Unless specified, all reagents, starting materials, and solvents were purchased from commercial sources and used as received. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed using precoated silica gel plates and visualization was achieved by UV light (254 nm). Flash chromatography was performed using silica gel and a gradient solvent

system. ^1H and ^{13}C NMR spectra were measured on 400 or 600 MHz spectrometers with CDCl_3 as solvent. Chemical shifts (ppm) were recorded with respect to TMS in CDCl_3 . Multiplicities are given as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets) or dt (doublet of triplets). Coupling constants are reported as a J value in Hz. HRMS data were recorded on a mass spectrometer with electrospray ionization and TOF mass analyzer. Optical rotations were measured with a sodium lamp (589 nm) and a double-jacketed 10 cm cell at 25 °C. The chiral HPLC analyses were performed on Agilent 1260 Infinity unit (pump G1311B, autosampler G1329B, DAD G1315D). The analytical column (250 × 4.6 mm) used is (S,S)-Whelk-O1 from Regis Technologies (Morton Grove). Retention times R_t in minutes, retention factors $k_i = (R_{t_i} - R_{t_0})/R_{t_0}$ and enantioselectivity factor $\alpha = k_2/k_1$ and resolution $R_s = 1.18 (R_{t_2} - R_{t_1})/(w_1 + w_2)$ are given. Preparative chiral separations were done with (S,S)-Whelk-O1 from Regis Technologies (Morton Grove) with a mixture of heptane/ethanol/chloroform (7/2/1) as mobile phase.

General Synthesis of *N*-Arylthiazoline-2-thione. Distilled triethylamine (40 mmol) was added dropwise under nitrogen atmosphere to a solution of an *ortho*-substituted aniline (20 mmol) for series **1** or an *ortho,para*-disubstituted aniline (20 mmol) for series **2** in carbon disulfide (38 mL). The mixture was stirred 24–48 h at rt (2 h for **1k**). Then the precipitate was filtered, washed with Et_2O , and dried to give the dithiocarbamate salt. This salt was used without any further purification and immediately solubilized in acetonitrile (31 mL). 2-Chlorocyclopentanone (20 mmol) was then added dropwise at rt under nitrogen atmosphere. The mixture was stirred 24 h at rt. Then a 37% HCl solution (5 mL) was added dropwise, and the mixture was heated at reflux (oil bath) for 20 min. The solvent was evaporated under reduced pressure, and water was added (50 mL). The mixture was extracted with dichloromethane (3 × 50 mL), and the organic layer was dried on MgSO_4 and evaporated under reduced pressure. The desired product was purified by flash chromatography (petroleum ether–dichloromethane, 100/0 → 0/100).

3-(2-Fluorophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1a:** yield 79% (2.04 g); white solid; mp 130 °C (racemate); ^1H NMR (400 MHz, CDCl_3) δ 2.43–2.48 (4H, m, 2 CH_2), 2.79–2.81 (2H, m, CH_2), 7.24–7.32 (2H, m, arom), 7.38–7.43 (1H, m, arom), 7.45–7.51 (1H, m, arom); ^{19}F NMR (376.5 MHz) δ –119.8; ^{13}C NMR (100 MHz, CDCl_3) δ 25.4, 27.4, 28.3, 117.2 (d, $J = 19.3$), 123.4, 125.0 (d, $J = 4.0$), 125.4 (d, $J = 12.7$), 129.8, 131.5 (d, $J = 7.9$), 145.9, 157.0 (d, $J = 253.1$), 194.3; HRMS (ESI/TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{12}\text{H}_{11}\text{NS}_2\text{F}$ 252.0311, found 252.0309. Dynamic chiral HPLC: Chiralpak IA, 5 °C, heptane/ethanol 70/30, 1 mL/min, UV and CD 254 nm, $t_{R1} = 5.53$ min (+), $t_{R2} = 6.31$ min (–), chromatogram with plateau between the two peaks.

3-(2-Chlorophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1b:** yield 18% (1.39 g); white solid; $R_f = 0.78$ (dichloromethane); mp 158.1 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.36–2.55 (4H, m, 2 CH_2), 2.79–2.86 (2H, m, CH_2), 7.35–7.38 (1H, m, arom), 7.43–7.45 (2H, m, arom), 7.56–7.59 (1H, m, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 25.3, 27.3, 28.2, 123.3, 128.0, 129.7, 130.7, 130.9, 132.0, 135.4, 145.5, 193.7; HRMS (ESI/TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{12}\text{H}_{11}\text{NS}_2\text{Cl}$ 268.0016, found 268.0017. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, t_{R1} for (S_a)-**1b** = 6.48 min (+), t_{R2} for (R_a)-**1b** = 7.57 min (–), $k_1 = 1.16$, $k_2 = 1.52$, $\alpha = 1.31$, and $R_s = 3.04$. (S_a)-**1b** (first eluted enantiomer; 99.5% ee): $[\alpha]_D^{25} = -57$ (c 1.05, CHCl_3).

3-(2-Bromophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1c:** yield 70% (6.84 g); yellow solid; $R_f = 0.43$ (petroleum ether/dichloromethane, 1/1); mp 140 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.39–2.51 (4H, m, 2 CH_2), 2.78–2.84 (2H, m, CH_2), 7.34–7.38 (2H, m, arom), 7.48 (1H, td, $J = 1.6$, 8.0, arom), 7.75 (1H, dd, $J = 1.2$, 8.0, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 25.3, 27.3, 28.1, 121.7, 123.3, 128.7, 129.7, 131.0, 133.8, 137.0, 145.3, 193.4; HRMS (ESI/TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{12}\text{H}_{11}\text{NS}_2\text{Br}$ 311.9511, found 311.9511. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, $t_{R1} = 6.42$ min (–), t_{R2}

= 7.43 min (+), $k_1 = 1.14$, $k_2 = 1.48$, $\alpha = 1.30$, and $R_s = 2.85$. First eluted (98% ee): $[\alpha]_D^{25} = -5$ (c 1.03, CHCl_3).

3-(2-Iodophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1d:** yield 44% (4.39 g); orange solid; $R_f = 0.70$ (petroleum ether/dichloromethane, 7/3); mp 151 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.40–2.51 (4H, m, 2 CH_2), 2.79–2.85 (2H, m, CH_2), 7.20 (1H, td, $J = 1.5$, 7.8, arom), 7.32 (1H, dd, $J = 1.6$, 8.0, arom), 7.50 (1H, td, $J = 1.6$, 8.0, arom), 7.97 (1H, dd, $J = 1.2$, 8.0, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 25.4, 27.7, 28.2, 96.9, 123.6, 129.1, 129.7, 131.0, 140.2, 140.7, 145.1, 193.2; HRMS (ESI/TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{12}\text{H}_{11}\text{NS}_2\text{I}$ 359.9372, found 359.9374. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, $t_{R1} = 6.74$ min (+), $t_{R2} = 7.83$ min (–), $k_1 = 1.25$, $k_2 = 1.61$, $\alpha = 1.29$, and $R_s = 1.57$. Second eluted (99.5% ee): $[\alpha]_D^{25} = -79$ (c 1.29, CHCl_3).

3-(2-Methylphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1e:** yield 94% (9.48 g); brown solid; $R_f = 0.48$ (petroleum ether/dichloromethane, 1/1); mp 129 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.18 (3H, s, CH_3), 2.31–2.48 (4H, m, 2 CH_2), 2.79–2.83 (2H, m, CH_2), 7.14–7.16 (1H, m, arom), 7.30–7.40 (3H, m, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 17.6, 25.3, 27.4, 28.2, 123.4, 127.2, 127.3, 129.7, 131.3, 135.6, 136.8, 145.8, 192.8; HRMS (ESI/TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{NS}_2$ 248.0562, found 248.0562. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, $t_{R1} = 6.07$ min (+), $t_{R2} = 8.39$ min (–), $k_1 = 1.02$, $k_2 = 1.80$, $\alpha = 1.76$, and $R_s = 6.31$. First eluted (99.5% ee): $[\alpha]_D^{25} = +119$ (c 1.02, CHCl_3).

3-(2-Isopropylphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1f:** yield 59% (5.95 g); orange solid; $R_f = 0.38$ (petroleum ether/dichloromethane, 1/1); mp 110–111 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.15 (3H, d, $J = 9.2$), 1.29 (3H, d, $J = 9.2$), 2.35–2.42 (4H, m), 2.75 (1H, sep, $J = 9.2$), 2.79–2.82 (2H, m), 7.10 (1H, d, $J = 10.4$), 7.29–7.35 (1H, m), 7.47 (2H, d, $J = 5.6$); ^{13}C NMR (100 MHz, CDCl_3) δ 23.5, 23.8, 25.3, 27.6, 28.2, 28.3, 123.2, 127.0, 127.1, 127.4, 130.1, 135.5, 146.1, 146.2, 193.6; HRMS (ESI/TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{18}\text{NS}_2$ 276.0875, found 276.0876. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, $t_{R1} = 5.31$ min (+), $t_{R2} = 7.38$ min (–), $k_1 = 0.77$, $k_2 = 1.46$, $\alpha = 1.90$, and $R_s = 6.03$. First eluted (98.5% ee): $[\alpha]_D^{25} = +99$ (c 1.12, CHCl_3).

3-(2-Phenylphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1g:** yield 71% (3.53 g); brown solid; $R_f = 0.50$ (dichloromethane/petroleum ether, 7/3); mp 144–146 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.91–1.98 (2H, m, CH_2), 2.14–2.22 (2H, m, CH_2), 2.47–2.63 (2H, m, CH_2), 7.29–7.55 (9H, m, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 25.6, 27.8, 28.1, 123.3, 128.1, 128.6 (2 C), 128.7 (3 C), 129.5, 130.1, 131.5, 135.6, 137.9, 139.6, 146.5, 194.3; HRMS (ESI/TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{18}\text{H}_{16}\text{NS}_2$ 310.0719, found 310.0719. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, $t_{R1} = 6.15$ min (+), $t_{R2} = 7.12$ min (–), $k_1 = 1.05$, $k_2 = 1.37$, $\alpha = 1.30$, and $R_s = 2.65$. First eluted (98.5% ee): $[\alpha]_D^{25} = +57$ (c 1.28, CHCl_3).

3-(2-(Methoxymethyl)phenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1h:** yield 54% (1.78 g); brown solid; $R_f = 0.40$ (dichloromethane/petroleum ether, 7/3); mp 149–151 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.37–2.44 (4H, m, 2 CH_2), 2.79–2.83 (2H, m, CH_2), 3.32 (3H, s, CH_3), 4.35 (2H, s, CH_2); 7.16–7.19 (1H, dd, $J = 1.2$, 7.2, arom), 7.43–7.47 (1H, td, $J = 1.2$, 7.5, arom), 7.48–7.52 (1H, td, $J = 1.0$, 7.3, arom), 7.58–7.60 (1H, br d, $J = 7.36$, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 25.4, 27.5, 28.2, 58.7, 70.9, 123.1, 127.4, 129.2, 129.7, 129.9, 136.0, 136.4, 146.6, 193.0; HRMS (ESI/TOF) m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{14}\text{H}_{16}\text{NOS}_2$ 278.0668, found 278.0669. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, $t_{R1} = 6.72$ min (+), $t_{R2} = 9.53$ min (–), $k_1 = 1.24$, $k_2 = 2.18$, $\alpha = 1.76$, and $R_s = 6.74$. First eluted (98% ee): $[\alpha]_D^{25} = +190$ (c 1.08, CHCl_3).

3-(2-Aminophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]-thiazole-2-thione **1k:** yield 22% (3.22 g); brown oil; $R_f = 0.20$ (dichloromethane/petroleum ether, 7/3); ^1H NMR (400 MHz, CDCl_3) δ 2.35–2.58 (4H, m, 2 CH_2), 2.77–2.83 (2H, m, CH_2),

3.88 (2H, br s, NH₂), 6.86–6.88 (2H, br d, *J* = 7.6, arom), 7.02–7.05 (1H, dd, *J* = 1.6, 8.4, arom), 7.31–7.36 (1H, m, arom); ¹³C NMR (100 MHz, CDCl₃) δ 25.4, 27.7, 28.4, 117.9, 119.5, 124.1, 124.2, 127.6, 130.6, 142.7, 146.7, 191.8; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₂H₁₃N₂S₂ 249.0515, found 249.0515. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, *t*_{R1} = 7.51 min (+), *t*_{R2} = 10.22 min (–), *k*₁ = 1.55, *k*₂ = 2.47, α = 1.60, and Rs = 6.46. Second eluted (93% ee): [α]_D²⁵ –480 (c 0.19, CHCl₃).

3-(2-Dimethylaminophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1l: yield 97% (2.47 g); green solid; *R*_f = 0.60 (dichloromethane/petroleum ether, 7/3); mp 100–101 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.24–2.40 (3H, m, CH₂), 2.55–2.61 (1H, m, CH₂), 2.68 (6H, s, 2 CH₃), 2.74–2.86 (2H, m, CH₂); 7.00–7.09 (2H, m, arom), 7.26–7.29 (1H, dd, *J* = 1.6, 8.0, arom), 7.31–7.36 (1H, td, *J* = 1.4, 8.6, arom); ¹³C NMR (100 MHz, CDCl₃) δ 25.4, 27.4, 28.2, 42.7 (2C), 118.9, 121.3, 123.1, 129.0, 129.9, 130.1, 147.4, 149.1, 193.4; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₄H₁₇N₂S₂ 277.0828, found 277.0827. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV, *t*_{R1} = 5.93 min, *t*_{R2} = 7.09 min, *k*₁ = 0.98, *k*₂ = 1.36, α = 1.39, and Rs = 3.56. Second eluted (99% ee): [α]_D²⁵ +138 (c 1.05, CHCl₃).

3-(2-Methoxyphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1n: yield 96% (9.63 g); brown solid; *R*_f = 0.10 (dichloromethane/petroleum ether, 1/1); mp 151–152 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.38–2.49 (4H, m, 2 CH₂), 2.77–2.82 (2H, m, CH₂), 3.83 (3H, s, CH₃), 7.06–7.09 (2H, m, arom), 7.26–7.29 (1H, dd, *J* = 2.0, 8.4, arom), 7.42–7.46 (1H, td, *J* = 1.6, 8.4, arom); ¹³C NMR (100 MHz, CDCl₃) δ 25.3, 27.3, 28.2, 56.0, 112.7, 121.0, 122.6, 126.2, 129.2, 130.9, 146.7, 154.4, 193.7; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₃H₁₄NOS₂ 264.0511, found 264.0511; Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, *t*_{R1} = 7.17 min (–), *t*_{R2} = 9.66 min (+), *k*₁ = 1.39, *k*₂ = 2.22, α = 1.60, and Rs = 6.28.

3-(2-Thiomethoxyphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1q: yield 76% (7.58 g); white solid; *R*_f = 0.70 (dichloromethane/petroleum ether 1/1); mp 147–149 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.37–2.41 (3H, m, CH₂), 2.44 (3H, s, CH₃), 2.47–2.52 (1H, m, CH₂), 2.80–2.83 (2H, m, CH₂), 7.22 (1H, dd, *J* = 1.2, 7.6, arom), 7.29 (1H, td, *J* = 1.6, 8.0, arom), 7.39 (1H, dd, *J* = 1.6, 8.0, arom), 7.45 (1H, td, *J* = 1.6, 8.0, arom); ¹³C NMR (100 MHz, CDCl₃) δ 15.5, 25.4, 27.4, 28.3, 123.4, 126.1, 127.3, 128.5, 130.2, 135.6, 137.4, 145.9, 193.5; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₃H₁₄NS₂ 280.0283, found 280.0281. Chiral HPLC: Whelk-O1 (S,S), 25 °C, Heptane/ethanol 60/40, 1 mL/min, UV, *t*_{R1} = 7.17 min, *t*_{R2} = 9.20 min, *k*₁ = 1.39, *k*₂ = 2.07, α = 1.49, and Rs = 4.87. First eluted (99% ee): [α]_D²⁵ +52 (c 1.15, CHCl₃).

3-(Naphthalen-1-yl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1r: yield 54% (3.75 g); white solid; *R*_f = 0.25 (dichloromethane/petroleum ether, 1/1); mp 118.0–120.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.22–2.44 (4H, m, 2 CH₂), 2.83–2.87 (2H, m, CH₂), 7.47–7.62 (5H, m, arom), 7.94–8.00 (2H, m, arom); ¹³C NMR (100 MHz, CDCl₃) δ 25.3, 27.4, 28.3, 122.3, 123.3, 125.5, 125.9, 126.8, 127.6, 128.7, 129.0, 130.1, 134.4, 134.5, 146.7, 194.1; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₆H₁₄NS₂ 284.0562, found 284.0563. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, *t*_{R1} = 8.26 min (+), *t*_{R2} = 11.61 min (–), *k*₁ = 1.75, *k*₂ = 2.87, α = 1.64, and Rs = 6.89. Second eluted (97.5% ee): [α]_D²⁵ –181 (c 0.81, CHCl₃).

3-(Isoquinolin-5-yl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1s: yield 57% (1.51 g); brown solid; *R*_f = 0.30 (ethyl acetate/petroleum ether); mp 178.9–179.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.24–2.30 (1H, m, CH₂), 2.46–2.49 (3H, m, CH₂), 2.89–2.92 (2H, m, CH₂), 7.33 (1H, d, *J* = 5.6, arom), 7.69–7.77 (2H, m, arom), 8.13 (1H, d, *J* = 8.0, arom), 8.58 (1H, d, *J* = 5.6, arom), 9.37 (1H, s, arom); ¹³C NMR (100 MHz, CDCl₃) δ 25.3, 27.4, 28.3, 115.2, 123.9, 127.1, 129.4, 129.6, 130.4, 132.0, 133.6, 144.5, 146.0, 153.1, 194.3; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₅H₁₃N₂S₂ 285.0515, found 285.0516. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, *t*_{R1} = 17.67

min (+), *t*_{R2} = 23.13 min (–), *k*₁ = 4.99, *k*₂ = 6.84, α = 1.37, and Rs = 4.52. First eluted (99% ee): [α]_D²⁵ +193 (c 0.56, CHCl₃).

3-(Quinolin-8-yl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1t: yield 5% (0.13 g); brown solid; *R*_f = 0.30 (dichloromethane); mp 176.1–176.8 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.30–2.42 (4H, m, 2 CH₂), 2.78–2.93 (2H, m, CH₂), 7.46–7.49 (1H, dd, *J* = 4.4, 8.4, arom), 7.66–7.70 (1H, t, *J* = 7.7, arom); 7.82–7.84 (1H, dd, *J* = 1.6, 7.6, arom), 7.96–7.99 (1H, dd, *J* = 1.6, 8.4, arom), 8.23–8.26 (1H, dd, *J* = 2.0, 8.4, arom), 8.93–8.95 (1H, dd, *J* = 1.6, 4.0, arom); ¹³C NMR (100 MHz, CDCl₃) δ 25.3, 27.6, 28.2, 122.0, 122.7, 126.1, 129.5, 129.8, 129.9, 135.1, 136.3, 143.4, 147.4, 151.4, 194.2; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₅H₁₃N₂S₂ 285.0515, found 285.0514. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, *t*_{R1} = 8.11 min (–), *t*_{R2} = 10.51 min (+), *k*₁ = 1.70, *k*₂ = 2.50, α = 1.47, and Rs = 4.77. First eluted (86% ee): [α]_D²⁵ –139 (c 0.29, CHCl₃).

3-(2-Chloro-4-methylphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 2a: yield 95% (3.78 g); brown solid; *R*_f = 0.77 (dichloromethane); mp 175–176 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.41–2.54 (4H, m, 2 CH₂), 2.43 (3H, s, CH₃), 2.81–2.85 (2H, m, CH₂), 7.25–7.29 (2H, m, arom), 7.41 (1H, br s, arom); ¹³C NMR (100 MHz, CDCl₃) δ 21.3, 25.5, 27.5, 28.3, 123.3, 129.0, 129.3, 131.3, 131.6, 132.9, 141.7, 145.9, 194.0; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₃H₁₃NClS₂ 282.0172, found 282.0172. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 80/20, 1 mL/min, UV and CD 254 nm, *t*_{R1} = 8.56 min (+), *t*_{R2} = 10.55 min (–), *k*₁ = 1.85, *k*₂ = 2.52, α = 1.36, and Rs = 4.42. Second eluted (97% ee): [α]_D²⁵ +53 (c 1.00, CHCl₃).

3-(2-Chloro-4-fluorophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 2b: yield 96% (3.86 g); brown solid; *R*_f = 0.79 (dichloromethane); mp 147.1–148.9 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.39–2.55 (4H, m, 2 CH₂), 2.75–2.88 (2H, m, CH₂), 7.13–7.18 (1H, m, arom), 7.31–7.38 (2H, m, arom); ¹⁹F NMR (376.5 MHz) δ –108.0; ¹³C NMR (100 MHz, CDCl₃) δ 25.3, 27.3, 28.2, 115.5 (d, *J* = 22.6), 118.2 (d, *J* = 25.6), 123.4, 131.1 (d, *J* = 9.5), 131.6 (d, *J* = 3.8), 133.4 (d, *J* = 10.9), 145.3, 162.6 (d, *J* = 252.2), 194.1; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₂H₁₀NFS₂Cl 285.9922, found 285.9923. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, *t*_{R1} = 5.59 min (+), *t*_{R2} = 6.54 min (–), *k*₁ = 0.86, *k*₂ = 1.18, α = 1.37, and Rs = 2.71. First eluted (99% ee): [α]_D²⁵ –69 (c 1.14, CHCl₃).

3-(2-Methyl-4-methoxyphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 2c: yield 93% (7.00 g); brown solid; *R*_f = 0.60 (dichloromethane); mp 107–108 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.13 (3H, s, CH₃), 2.32–2.48 (4H, m, 2 CH₂), 2.78–2.81 (2H, m, CH₂), 3.82 (3H, s, CH₃); 6.82–6.86 (2H, m, arom), 7.05–7.08 (1H, d, *J* = 8.4); ¹³C NMR (100 MHz, CDCl₃) δ 18.1, 25.5, 27.7, 28.4, 55.6, 112.7, 116.6, 123.2, 128.4, 129.8, 137.1, 146.4, 160.3, 193.4; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₄H₁₆NOS₂ 278.0668, found 278.0669. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV, *t*_{R1} = 7.41 min, *t*_{R2} = 15.20 min, *k*₁ = 1.47, *k*₂ = 4.07, α = 2.77, and Rs = 11.76. First eluted (99% ee): [α]_D²⁵ +83 (c 0.19, CHCl₃).

3-(2-Methyl-4-fluorophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 2d: yield 98% (4.15 g); brown solid; *R*_f = 0.78 (dichloromethane/ethyl acetate 9/1); mp 114.1–114.7 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.16 (3H, s, CH₃), 2.33–2.46 (4H, m, 2 CH₂), 2.79–2.83 (2H, m, CH₂), 6.99–7.08 (2H, m, arom), 7.12–7.16 (1H, dd, *J* = 5.2, 8.6, arom); ¹⁹F NMR (376.5 MHz) δ –111.4; ¹³C NMR (100 MHz, CDCl₃) δ 17.9, 25.3, 27.5, 28.3, 114.3 (d, *J* = 22.7), 118.2 (d, *J* = 22.5), 123.5, 129.0 (d, *J* = 9.2), 132.7 (d, *J* = 3.0), 138.3 (d, *J* = 8.7), 145.7, 162.8 (d, *J* = 247.8), 193.3; HRMS (ESI/TOF) *m/z* [M + H]⁺ calcd for C₁₃H₁₃NFS₂ 266.0468, found 266.0471. Chiral HPLC: Whelk-O1 (S,S), 25 °C, heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, *t*_{R1} = 5.77 min (+), *t*_{R2} = 8.32 min (–), *k*₁ = 0.92, *k*₂ = 1.77, α = 1.92, and Rs = 6.42. First eluted (96% ee): [α]_D²⁵ +108 (c 0.98, CHCl₃).

3-(2-Hydroxyphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1m. To a solution of 3-(2-methoxyphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1n (100 mg, 0.38

mmol) in anhydrous dichloromethane (4.50 mL) was added dropwise a solution of BBr_3 (3.80 mmol, 0.37 mL) in anhydrous dichloromethane (4.50 mL) at -78°C under nitrogen atmosphere. After complete addition, the mixture was warmed to room temperature and stirred overnight. The mixture was added to an aqueous solution of 5% NaCl (15 mL). The mixture was extracted with dichloromethane (3×10 mL), and the organic layer was washed with a solution of NaHCO_3 , dried on MgSO_4 and evaporated under reduced pressure to give the desired product: yield 96% (90 mg); brown solid; $R_f = 0.20$ (dichloromethane/petroleum ether, 7/3); mp $146\text{--}147^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 2.36–2.48 (3H, m, CH_2+CH), 2.74–2.84 (3H, m, CH_2+CH), 6.68 (1H, br s, OH), 7.06–7.09 (1H, br t, $J = 8.0$, arom), 7.12–7.14 (1H, dd, $J = 1.6, 7.9$, arom), 7.19–7.21 (1H, br d, $J = 7.4$, arom), 7.38–7.43 (1H, dt, $J = 1.6, 8.4$, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 25.6, 28.2, 28.3, 121.3, 121.9, 125.9, 126.3, 126.9, 130.9, 147.2, 150.8, 190.6; HRMS (ESI/TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{12}\text{NOS}_2$ 250.0355, found 250.0355; Dynamic chiral HPLC: Whelk-O1 (S,S), 25°C , heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, $t_{R1} = 4.89$ min (–), $t_{R2} = 6.08$ min (+), $k_1 = 0.63$, $k_2 = 1.03$, chromatogram with plateau between the two peaks.

3-(2-Trifluoromethylphenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1j. To a solution of 2-trifluoromethylaniline (1.26 mL, 10 mmol) in DMSO (4 mL) was added sodium hydroxide (0.40 g, 10 mmol) under nitrogen atmosphere. After 15 min of stirring at room temperature, carbon disulfide (0.60 mL, 10 mmol) was added at 0°C . The mixture was stirred 60 min at room temperature, 2-chlorocyclopentanone (1 mL, 10 mmol) was added at 0°C , and the mixture was stirred overnight at rt. The mixture was then diluted with 100 mL of water and extracted with dichloromethane (3×40 mL), and the organic layer was dried on MgSO_4 and evaporated under reduced pressure. The crude was purified by flash chromatography (petroleum ether–dichloromethane, 100/0 \rightarrow 65/35) to give the desired product: yield 2.5% (75 mg); yellow solid; $R_f = 0.60$ (dichloromethane/petroleum ether, 7/3); mp $137\text{--}138^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 2.33–2.50 (4H, m, 2 CH_2), 2.76–2.86 (2H, m, CH_2), 7.36 (1H, br d, $J = 7.8$, arom), 7.64 (1H, br t, $J = 7.7$, arom), 7.74 (1H, dt, $J = 0.5, 7.8$, arom), 7.86 (1H, dd, $J = 0.4, 7.7$, arom); ^{19}F NMR (376.5 MHz) δ -61.0 ; ^{13}C NMR (150 MHz, CDCl_3) δ 25.4, 27.3, 28.2, 122.6 (q, $J = 272.4$), 123.4, 127.9 (q, $J = 5.0$), 128.0 (q, $J = 31.5$), 130.1, 130.7, 133.5, 135.7, 145.8, 195.0; HRMS (ESI/TOF) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{11}\text{NS}_2\text{F}_3$ 302.0280; Found 302.0280. Chiral HPLC: Whelk-O1 (S,S), 25°C , heptane/ethanol 60/40, 1 mL/min, UV and polarimeter, $t_{R1} = 5.52$ min (–), $t_{R2} = 6.40$ min (+), $k_1 = 0.87$, $k_2 = 1.17$, $\alpha = 1.34$, and $R_s = 3.10$. Second eluted (97% ee): $[\alpha]_D^{25} +92$ (c 0.33, CHCl_3).

Procedure for Cyano (1i), Diphenylphosphino (1o), and Diphenylphosphoryl (1p) Derivatives. A solution of *n*-Butyllithium in hexanes (1.60 M, 0.53 mmol) was added dropwise at -78°C (ethanol bath) under nitrogen atmosphere to a solution of 3-(2-bromophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1c (0.48 mmol) in anhydrous THF (2.4 mL). Then a solution of chlorodiphenylphosphine for 1o (0.58 mmol), diphenylphosphinic chloride for 1p (0.58 mmol) or 1-cyanobenzimidazole for 1i (2.12 mmol) in anhydrous THF (0.3 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature (cooling bath was not removed) and stirred overnight. The solvent was removed under reduced pressure, and the crude was purified by flash chromatography (petroleum ether–dichloromethane, 100/0 \rightarrow 0/100) followed by chiral chromatography on Whelk-O1 (S,S) (heptane/ethanol/chloroform; 7/2/1).

3-(2-Cyanophenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1i: yield 20% (25.3 mg); brown solid; $R_f = 0.30$ (dichloromethane/petroleum ether, 7/3); mp $234\text{--}235^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 2.39–2.64 (4H, m, 2 CH_2), 2.76–2.8 (2H, m, CH_2), 7.49–7.51 (1H, dd, $J = 0.8, 8.0$, arom), 7.59–7.63 (1H, dt, $J = 1.2, 7.6$, arom), 7.76–7.80 (1H, td, $J = 1.6, 8.0$, arom), 7.84–7.86 (1H, dd, $J = 1.2, 7.6$, arom); ^{13}C NMR (100 MHz, CDCl_3) δ 25.4, 27.5, 28.2, 112.3, 115.1, 124.3, 129.6, 130.0, 134.0, 134.1, 140.0, 144.7, 194.4; HRMS (ESI/TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{11}\text{N}_2\text{S}_2$ 259.0358, found 259.0358. Chiral HPLC: Whelk-O1 (S,S), 25°C ,

Heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, $t_{R1} = 8.80$ min (+), $t_{R2} = 10.96$ min (–), $k_1 = 1.96$, $k_2 = 2.65$, $\alpha = 1.35$, and $R_s = 2.31$. First eluted (97% ee): $[\alpha]_D^{25} +4$ (c 0.24, CHCl_3).

3-(2-(Diphenylphosphino)phenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1o: yield 39%, (67.2 mg); yellow solid; $R_f = 0.60$ (dichloromethane/petroleum ether, 7/3); mp $199\text{--}200^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 1.61–1.69 (1H, m, CH_2), 1.93–1.98 (1H, m, CH_2), 2.13–2.20 (2H, m, CH_2), 2.64–2.67 (2H, m, CH_2), 7.18–7.50 (14H, m, arom); ^{31}P NMR (162 MHz, CDCl_3) δ -17.3 (s); ^{13}C NMR (100 MHz, CDCl_3) δ 25.6, 27.6, 28.2, 123.1, 128.1 (2 C, d, $J = 2.9$), 128.5 (d, $J = 6.2$), 128.7–128.8 (3 C), 129.4, 130.0, 130.9, 133.4 (2 C, d, $J = 19$), 134.5 (2 C, d, $J = 21.9$), 135.8 (d, $J = 12.7$), 135.9, 136.1 (d, $J = 11.3$), 138.3 (d, $J = 17.1$), 142.6 (d, $J = 26.2$), 146.4, 194.0; HRMS (ESI/TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{NPS}_2$ 418.0848, found 418.0848. Chiral HPLC: Whelk-O1 (S,S), 25°C , heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, $t_{R1} = 6.96$ min (+), $t_{R2} = 10.68$ min (–), $k_1 = 1.32$, $k_2 = 2.56$, $\alpha = 1.94$, and $R_s = 6.82$. First eluted (99% ee): $[\alpha]_D^{25} +100$ (c 0.86, CHCl_3).

3-(2-(Diphenylphosphoryl)phenyl)-3,4,5,6-tetrahydro-2H-cyclopenta[d][1,3]thiazole-2-thione 1p: yield 52% (238.7 mg); yellow solid; $R_f = 0.25$ (dichloromethane/ethyl acetate); mp $157\text{--}158^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 2.21–2.40 (3H, m, CH_2), 2.54–2.65 (2H, m, CH_2), 2.82–2.89 (1H, m, CH_2), 7.30–7.80 (14H, m, arom); ^{31}P NMR (162 MHz, CDCl_3) δ 25.8 (s); ^{13}C NMR (100 MHz, CDCl_3) δ 25.2, 27.8, 27.9, 122.9, 128.2–128.5 (3 C), 129.5 (d, $J = 11.6$), 130.8 (d, $J = 39.5$), 130.8 (d, $J = 7.3$), 131.2 (d, $J = 10.2$), 131.6–132.0 (6 C), 132.2 (C), 133.3–133.4 (2C), 135.5 (d, $J = 9.1$), 140.5 (d, $J = 1.8$), 146.9, 194.0; HRMS (ESI/TOF) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{NOP}_2$ 434.0797, found 434.0797; Chiral HPLC: Whelk-O1 (S,S), 25°C , heptane/ethanol 60/40, 1 mL/min, UV and CD 254 nm, $t_{R1} = 9.26$ min (–), $t_{R2} = 13.30$ min (+), $k_1 = 2.09$, $k_2 = 3.43$, $\alpha = 1.64$, and $R_s = 5.91$. First eluted (99% ee): $[\alpha]_D^{25} -71$ (c 0.17, CHCl_3).

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