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Combined Theoretical and Experimental Study on High Diastereoselective Chirality Transfer Based on [2.2]Paracyclophane Derivative Chiral Reagent

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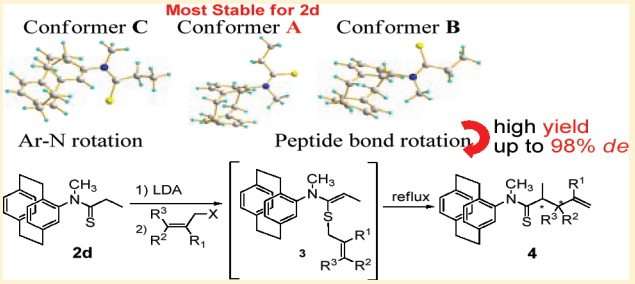
Supporting Information

ABSTRACT: We report a paracyclophane N−Me thioamide chiral reagent for the asymmetric thio-Claisen rearrangement with high diasteroselectivity. Comparisons between candidate chiral reagent N-phenyl-N-([2.2]paracyclophan-4-yl)amide, N-methyl amide, N-phenyl thioamide, and N-methyl thioamide are made both by experiment and theoretical calculations to clarify the principle behind the high diasteroselectivity. Dynamic ^{1}H NMR phenomenon tested by varying temperature (VT) experiments has proved that N−Ph amides have triple splitting peaks, while N−Ph thioamide would reduce the number to two, further substituting the Ph to Me made dynamic phenomenon disappear. So the side chain is thought to be the most rigid in N−Me thioamide, which accounts for a structure prerequisite favoring high efficient chirality transfer. This is confirmed by theoretical calculation: remarkable energy difference exists between the *Re* and *Si* faces of the chiral molecule. To further clarify the possible pathways for thio-Claisen rearrangement, theoretical prediction is adopted. The result implies that the cisoid pathways will dominate the process. Further experiment confirmed this: with N−Me thioamide, the asymmetrical reaction affords γ-unsaturated thioamides in good yields and high diastereoselectivities up to 98%. After removing the thioamide auxiliaries under hydrolysis conditions, product β,γ-substituted chiral alcohols reached high enantiopurity of 98% *ee*.



INTRODUCTION

Asymmetric synthesis is playing a crucial role in modern molecular synthesis for the past several decades.[1,2] As an indispensible part of the asymmetric process, effective chiral auxiliary should provide a suitable chiral environment as well as a rigid side chain to warrant high stereoselectivity.[3−5] So it has become a fundamental objective for researchers to find the ideal chiral auxiliary molecules.

The Claisen rearrangement is among the most powerful reactions for stereoselective construction of carbon−carbon bonds.[6] So researchers have paid lasting effort to its development. For aza-Claisen rearrangement, (*S*)-proline derivative auxiliaries[7,8] usually led to a moderate diastereoselectivity (up to 87%*de*). Compared to them, N-α-methylbenzyl auxiliaries could reach much better results[9](98%*de*). Several early attempts ignited the spark on stereoslective thio-Claisen rearrangement.[10−13] As central chiral auxiliaries, nonracemic thiolactam[14,15] (up to 98%*de*), enantiopure alkylsulfinyl group[16] (up to 100%*de*), and 2,5-diphenylpyrrolidine[17](up to 99%*de*) were used to control the stereochemistry. Later, axially chiral N-aryl thioamide[18](up to 72%*de*) was applied in asymmetric thio-Claisen rearrangement. The above works are all valuable and illuminating. However, none of them tried the planar chiral molecules, which might be more chemically stable and would be never subject to racemization even in harsh reaction conditions. In fact, efficient control of the stereochemistry in the Diels−Alder,[19] aldol,[19] Michael,[19,20] alkylation,[21] addition,[22−24] reduction,[24] and [2,3] sigmatropic rearrangement[25] reactions by means of planar chiral paracyclophane derivatives has all been reported. It thus prompted us to explore the possibility to take the paracyclophane skeleton as a chirial auxiliary for asymmetric [3,3]sigmatropic shifts. To the best of our knowledge, no structures with planar chirality have previously been used to induce the asymmetric Claisen rearrangement.

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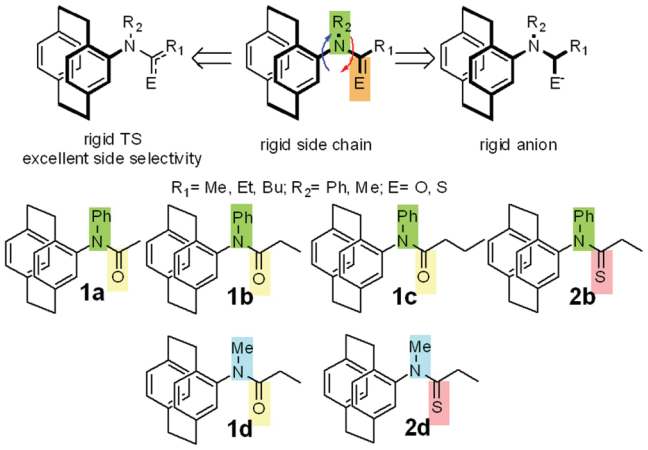
So in our work, we listed six planar paracyclophane based chirial auxiliary candidates and tried to find the best functional structures for Claisen rearrangement (see Scheme 1).

Scheme 1. Candidates for VT NMR Study To Obtain a Rigid Side Chain



Combining theoretical and experimental studies we have successfully screened out the best molecule. The diastereoselectivity has reached up to 98%*de*. Beside this, this work also provides a valuable example, which might be widely applicable for screening out the best chiral candidate with high efficiency and low cost.

RESULTS AND DISCUSSION

VT Experiment with C–N Bond Rotation. Varying temperature nuclear magnetic resonance (VT NMR) is an effective instrument for the study of bond rotation. To predict the best molecular that might favor high efficient chiral transfer, a series of VT ^{1}H NMR test is applied first to the six candidate molecules. This test makes it possible to unveil bond rotation in the form of dynamic NMR phenomenon due to their complicated magneto-chemistry factor.[26−28]

The VT ^{1}H NMR spectra of N-phenyl amide of paracyclophane (**1a**) is shown in Figure 1. There is an obvious change of the peak shape belonging to the methyl group. Started from 65 °C to ambient in *d*-DMSO, the peak gradually broadens. Three peaks appear at 5 °C in *d*-chloroform (peaks a, b, and c in Figure 1), whereas peaks b and c coalesce and show two signals, indicating that peaks a and c are of unequal intensity at −15 °C. An analogous phenomenon exists in the ^{1}H NMR of thioamides shown as **2b**, but the phenomenon seems less complicated. Peak d splits into two at 70 °C (peaks d and e in Figure 1). The most probable reason is bond rotation of the molecules in certain solvents, which was confirmed by experiments on the exchange correlation spectrometry (EXSY) of **1c** (see page S5 of the Supporting Information). Compared to **1a**/**b**/**c** and **2d**, no dynamic phenomena appears on the spectra of both amide **1d** and thioamide **2d**, and even the cooling temperature reaches −85 °C in *d*-methylene chloride. The results thus reflected the bond rigidity of each side chain. Since bond rigidity is directly linked to high efficient chiral transfer, the one with the rigid side chain may be molecular **1d** and **2d**.

Employing the Gutowsky-Holm equation ($k_c = 2^{-1/2}\pi\Delta\nu$) and the Erying equation ($\Delta G^{\ddagger}=RT_c[\ln T_c-\ln k_c+23.76]$),[29,30] we

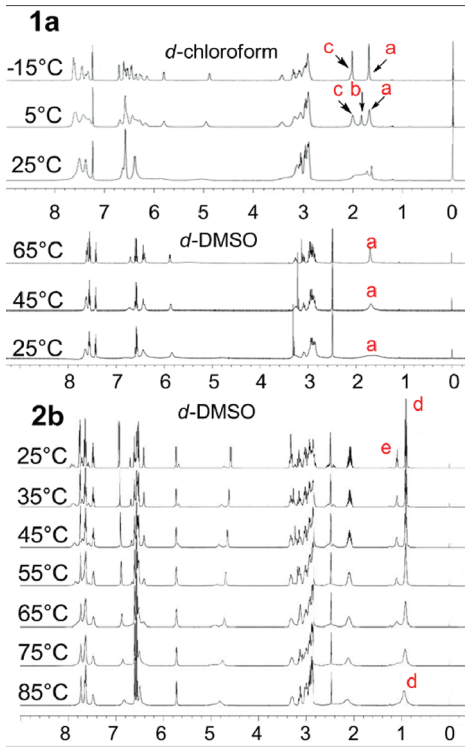


Figure 1. Variable-temperature ^{1}H NMR study of amide **1a** and thioamide **2b** (heating experiment in *d*-DMSO, cooling experiment in *d*-chloroform).

obtained the experimental free energies of activation $\Delta G^{\ddagger}$ (Table 1). It shows that bulky groups would contribute to

Table 1. Dynamic ^{1}H NMR Data for Amides and Thioamide in *d*-DMSO

compd	δ (ppm)[a]	T_{lowest} (K)	$\Delta\nu$ (Hz)	T_c (K)	k_c (s^{-1})	$\Delta G^{\ddagger}_{exp}$ (kcal/mol)[b]
1a	2.50, 1.74	218.15	228	298.15	506.49	13.8
1b	1.12, 0.90	218.15	96	303.15	213.25	14.5
1c	2.50, 1.89	218.15	183	358.15	406.52	16.8
2b	1.24, 1.05	298.15	63	348.15	139.95	17.1

[a]Chemical shift of CH_3 group. [b]Margin of error ±0.2 kcal/mol.

increase the rotation barriers and that substituting an oxygen (**1b**) atom for sulfur (**2b**) would also increase the $\Delta G^{\ddagger}$ value. The rigid skeleton of these compounds has restricted bond rotation of auxiliary part. Among all of the rest of the bonds, only peptide and Ar–N bonds are potential candidates for restricted rotation. Based on the recognition from the steady state of the molecules, we next can move on to their dynamic properties for more insightful information (Scheme 2).

Energy Profiles of C–N Bond Rotation. Energy profile for the internal rotation of **1b** and **2b** in chloroform is displayed in Scheme 2a. Different conformations in crystals of **1b** and **2b** lead to different relative conformations in local minima by flexible PES scanning of both peptide and Ar–N bonds (see pages S20–S28 of the Supporting Information for details). For each compound, both free energies of transition state A-B (TS_{AB}) and of conformer **B** are slightly higher than

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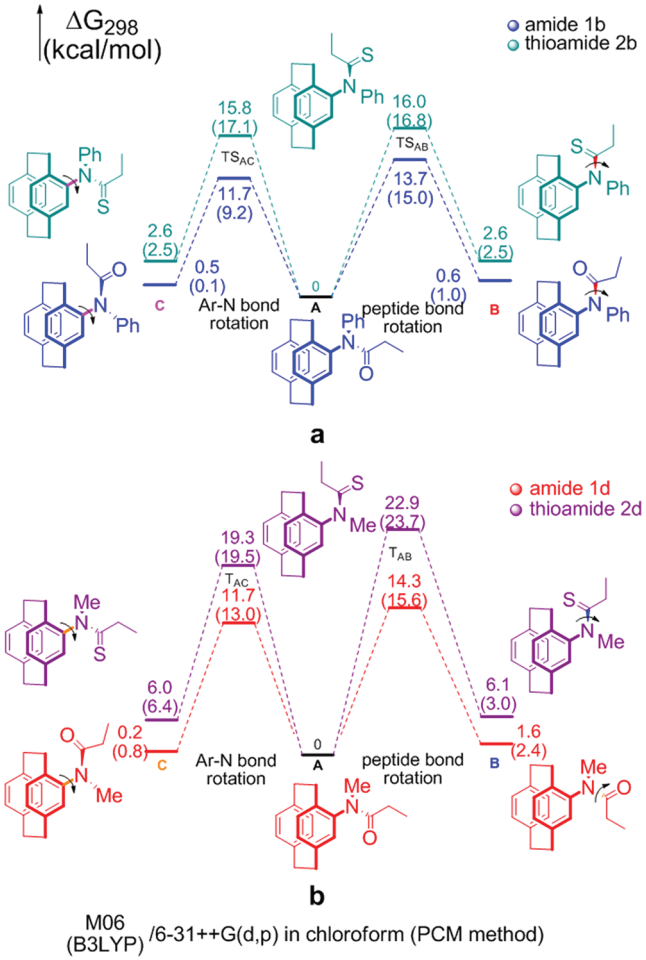
Scheme 2. Energy Profiles of Bond Rotations of Amide 1b/d and Thioamide 2b/d in *d*-Chloroform



corresponding free energies of TS_{AC} and conformer **C**. This indicates that peptide-type rotation is easier than Ar−N-type rotation. Moreover, free energies of the TSs and internal-rotation conformers of thioamide **2b** are also higher than that of amide **1b**, which is inconsistent with the experimental fact that dynamic NMR phenomena in amide **1b** are more obvious and complicated than that in thioamide **2b**.

Energy profiles for internal rotation of **1d** and **2d** in chloroform are shown in Scheme 2b. For the methyl case, amide **1d** seems to have no obvious difference in comparison with **1b** in terms of Gibbs energy. The Ar−N rotation for amide **1b** proved to be rotation with the lowest barrier, whereas peptide bond rotation for thioamide **2d** is validated with the highest barrier.

In Scheme 2, free energy of all conformers was calculated under the level of B3LYP and M06. The invariant relative energy sequence among conformers **A**/**B**/**C** and rotational TSs reveals the major factor of steric and electrostatic effects in the rotation process. The majority of energy barriers slightly decrease, and yet barriers of amide T_{AC} process increase, whereas other barriers decrease after consideration of correlation. The explanation is that n-π interaction between paracyclophane and amide O atom leads to destabilization. For the thioamides, the corresponding interaction is weakened for an increased length of C═S bonds.

NMR spectra were calculated employing the Gauge-Including Atomic Orbital (GIAO) method[31] based on the empirical in WP04/6-311++G(d,p) correction.[32] The quality of ^{1}H NMR chemical shifts description is comparable with the widely used B3LYP/6-311++G(2d,p) approach. Both experimental and computational data support the finding that all three conformers exist in amide **1b** solution (see Table 2).

Table 2. Computational and Experimental ^{1}H NMR Data for Amides 1b/d and Thioamide 2b[a]

	conformers				
compounds	A	B	C	exp.	solvents
1b	1.22	1.11	1.04	1.12, 0.90	*d*-DMSO
2b	0.96	1.13	1.13	1.24, 1.05	*d*-DMSO
1d	1.05	0.88	0.93	0.88	*d*-$CHCl_3$
2d	0.86	1.21	1.21	0.93	*d*-$CHCl_3$

[a]The calculation was made under the level of WP04/6-311++G(d,p) with the PCM-SCRF method.

Spectral peaks of conformer **A** and **C** coalesce at ambient temperature, and they coalesce with conformer **B** at higher temperature. Dynamic NMR spectra for thioamide **2b** also results from restricted rotation of the peptide bond because TS_{AB} is more kinetically favored than TS_{AC}. Thus, as for thioamide **2b**, only conformers **A** and **B** exist in the solvent, which is also in agreement with the experimental data (peaks a, b, c, d, e in Figure 1).

Nevertheless, amide **1d** bearing similar Gibbs energy surface with **1b** shows no splitting peaks on dynamic NMR spectrum. After consideration of every conformer, we found that the ethyl group of either amide **1b** or thioamide **2b** lies in the shielding zone of paracyclophane as well as deshielding zone of the phenyl group simultaneously and vice versa; while amide **1d**'s ethyl group always remains in the deshielding zone of paracyclophane cage. In addition, chemical shifts of amide **1d** distribute narrower than that of amide **1b**. The latter involves in more complicated magnetic environment than the former, which implies the origin of single peak.

From Scheme 2b, such a large energy difference between conformers **A** and **C** makes Ar−N flip forbidden and large $\Delta G^{\ddagger}$ of TS_{AB} makes peptide bond rotation restrained. Conformer **A** has a dominant population among all possible conformers, and therefore no dynamic NMR effect is observed in this case, either. On the basis of Boltzmann distribution, two conformations with an energy difference of at least 4.0 kcal/mol can just establish dominance (99.9%). The nonrotatable peptide and Ar−N bonds of thioamide **2d** establish a rigid side chain. Different chemical surroundings of the two chiral faces of the side chain are likely to lead to chirality transfer in proper asymmetric reactions.

In combination, the fourth conformation may exist in the solvent, which should go through a further rotation from conformer **B** or **C**. However, kinetic and thermodynamic factor results in minor population of **B** and **C**, which implies the fourth conformation would have an even smaller chance to present in chloroform. Both NMR calculation and experimental spectroscopy results show at most triplet peaks, which implies the fourth conformation is unfavorable.

The hypothesis now is that a rigid electroneutral side chain can also lead to a rigid electronegative sulfur anion and so a stable transition state. Planar-chiral [2.2]paracyclophane auxiliary provides different stereochemical surrounding of

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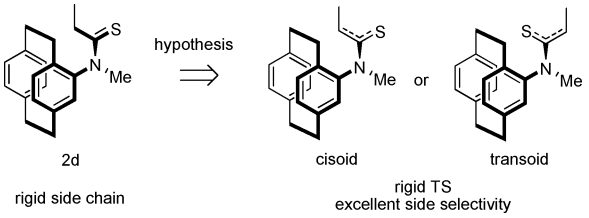
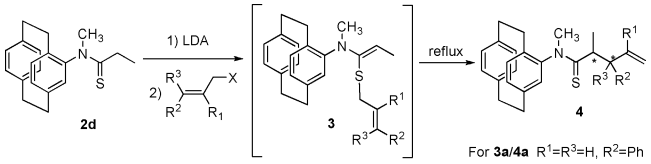
both *Re* and *Si* faces, which might lead to excellent chirality transfer for some asymmetric reactions involved in face selectivity (see Scheme 3).

Scheme 3. Hypothesis and Inference



Theoretical Prediction and Experiment of Asymmetric Thio-Claisn Arrangement. The assessment of thioamide **2d** in the thio-Claisen rearrangement should involve both the theoretical and experimental aspects (see Scheme 4). Most

Scheme 4. Thio-Claisen Rearrangement of Thioamide (R_p)-2d



early research tried to make clear the structure of TS in the thio-Claisen rearrangement, and they concluded that, in most circumstances, the reaction should be a concerted process via chairlike conformation.[33−38] In theoretical part, our task is searching all possible "chair-like" reaction paths to find the most probable one and then confirm the prediction by experiments.

Based on the above rational, four possible reaction pathways of two conformers of **3a** (transoid or cisoid relative to the thiocarbonyl group and N−Me bond) are explored. The corresponding energy profiles are shown in Scheme 5. All the calculated energies are relative to **cis-3a**, which is the lowest energy. From the profile, the reactant **3a** may react as either cisoid or transoid conformer divided only by a relatively small energy difference. Then each conformer may pass two distinct TSs, because the asymmetric process may go through both *Re* and *Si* faces of the thiocarbonyl group, respectively. The calculation was made under B3LYP and M06 methods respectively and invariant relative energy sequence was afforded, but energy difference was changed more or less after correlation interaction was considered.

First, for the reaction of transoid **3a** (Path A), the energy difference between the *Re* side and the *Si* face is 0.6 kcal/mol. Trans-**3a** can go through both TS-trans-I and TS-trans-II to afford two diastereoisomers. The $\Delta G^{\ddagger}$ of TS-trans-I is 20.6 kcal/mol, and cinnamyl group lies at the *Re* face of the thiocarbonyl group. The favored trans-(R_p, *R*, *R*)-**4a** can adjust its conformation to afford the most stable cisoid one. $\Delta G^{\ddagger}$ of TS-trans-II is 20.0 kcal/mol, and the cinnamyl group locates at the *Si* face of the thiocarbonyl group. Trans-(R_p, *S*, *S*)-**4a** also transforms into a cisoid disfavored product. Then for the reaction of cisoid **3a** (Path B), the two TS have a considerable energy gap (2.0 kcal/mol), which lead the reaction of cisoid exclusively to the favored product. On one hand, the favored cis-(R_p, *R*, *R*)-**4a** can be afforded via TS-cis-I with 16.4 kcal/mol as $\Delta G^{\ddagger}$. For TS-cis-I, the cinnamyl group locates at the *Re* face of the thiocarbonyl group. On the other hand, cis-**3a** can afford disfavored trans-(R_p, *S*, *S*)-**4a** via TS-cis-II with 18.4 kcal/mol as $\Delta G^{\ddagger}$. For TS-cis-II, the cinnamyl group locates at the *Si* face of the thiocarbonyl group.

An energy gap between both stable products cis-(R_p, *R*, *R*)-**4a** and cis-(R_p, *S*, *S*)-**4a** (ΔG=5.3 kcal/mol) indicates four late transition states. After comparison of those late transition states, a conclusion might be drawn that the thio-Claisen rearrangement can only go through Path B to afford corresponding diastereoisomers. A large energy difference between TS-Cis-I and II ($\Delta\Delta G^{\ddagger}$=2.0 kcal/mol) also ensures excellent diastereoselectivity. In terms of experiment, propanethioamide **2d** is the simplest thioamide used in the asymmetric thio-Claisen rearrangement; chiral 4-amine-paracyclophane is also the simplest planar chiral paracyclophane amine; and the methyl group of the nitrogen substituent is also the smallest

Scheme 5. Two Possible Pathways of Asymmetric Thio-Claisen Rearrangement (in THF)

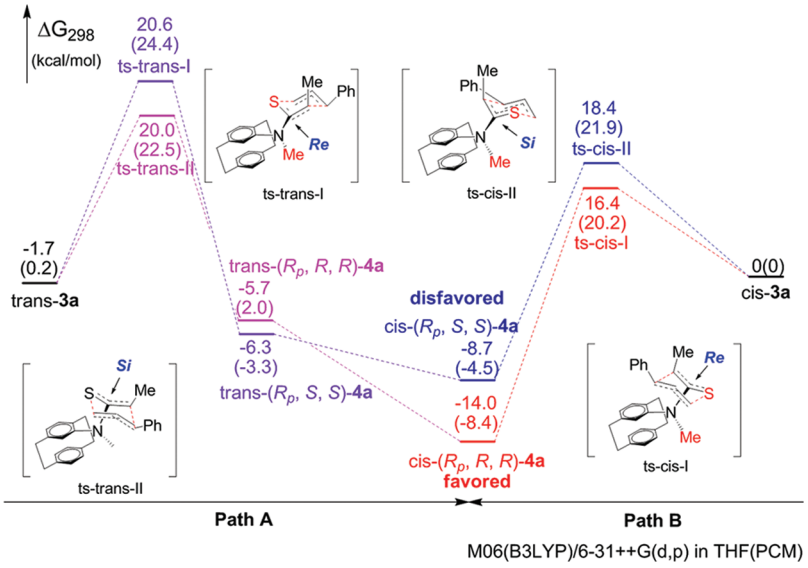


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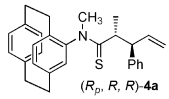
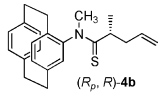
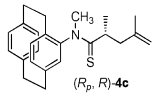
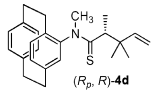
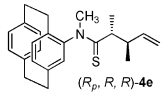
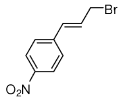
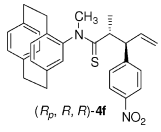
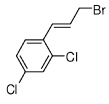
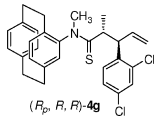
Table 3. Thio-Claisen Rearrangement of Thioamide (R_p)-2d[a]

Entry	Allyl halide	Product[b]	Yield[c]	*de*[d]
1		 (R_p, *R*, *R*)-**4a**	91%	98%
2		 (R_p, *R*)-**4b**	97%	91%
3		 (R_p, *R*)-**4c**	91%	90%
4		 (R_p, *R*)-**4d**	86%	74%e
5		 (R_p, *R*, *R*)-**4e**	74%	--f
6		 (R_p, *R*, *R*)-**4f**	87%	96%
7		 (R_p, *R*, *R*)-**4g**	74%	98%

[a]THF, LDA, 0 °C; then add allylic halide, and then reflux. [b]The absolute configurations of the rearrangement products were assigned by X-ray analysis of **4b**, **4c**, and **4e** and by ^{1}H NMR correlation with other rearrangement products. [c]Isolated yield. [d]The diastereoselectivities (*de*) were determined by ^{1}H NMR. [e]The diastereoselectivities (*de*) were determined by HPLC. [f]Used 85% pure Z-crotyl bromide (remainder 3-bromo-1-butene); the diastereoselectivities (*de*) could not be determined by ^{1}H NMR or HPLC.

substituent, which would minimize its influence on the transition state during rearrangement. The designed chiral thioamide auxiliary (R_p)-**2d** was readily prepared from (R_p)-paracyclophane-4-amine in good yields via a four-step sequence.

Experiments to probe the generality of the reaction are summarized in Table 3. The examples of asymmetric thio-Claisen rearrangement with the asymmetric center created in the α-position to the thiocarbonyl group were tested first (entries 2−4, Table 3). Treatment of thioamide (R_p)-**2d** with allyl bromide easily afforded the thio-Claisen rearrangement product **4b** in nearly quantitative yield with good diastereoselectivities (*de*), with a 3:0.14 ratio (91% *de*). Similar selectivity and activity were observed for the S-allylation rearrangement using methallyl chloride: **4c** was obtained in 91% yield with 90% *de*. The yield and the *de* of **4d** decreased to 86% and 74%, respectively, for 4-chloro-2-methyl-2-butene. Next, the asymmetric centers created simultaneously in the positions α- and β- to the thiocarbonyl group of the thio-Claisen rearrangement using four E-allyl bromides were examined (entries 1, 5−7, Table 3). The rearrangement of E-crotyl bromide (remainder 3-bromo-1-butene) did not produce a satisfactory determination of the diastereoisomeric excess. To our pleasant surprise, the product **4a** of E-cinnamyl bromide was obtained in 91% yield with 98% *de*. Two other cinnamyl bromide derivatives were also successfully employed in the thio-Claisen rearrangement with high diastereoselectivities.

The absolute configurations of the newly created centers in the rearrangement products were assigned by X-ray diffraction analysis of **4b**/**4c** and by ^{1}H NMR correlation with other rearrangement products (Figure 2). All the absolute configurations of the newly created asymmetric centers in the α-position and β-position to the thiocarbonyl group in the major diastereomers were determined to be in the *R* configuration.

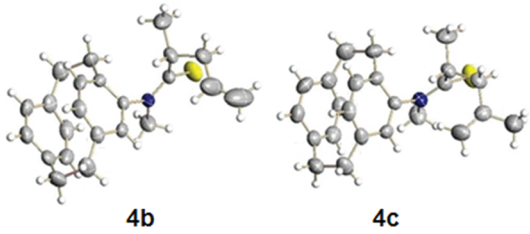


Figure 2. The X-ray structures of **4b** and **4c**.

Removal and Recycle of Auxiliary. The chiral auxiliary can be cleaved from the products **4a** and **4f** under reductive hydrolysis conditions (Scheme 6), and β,γ-substituted chiral alcohols (*R*, *R*)-**5a** and (*R*, *R*)-**5f** were obtained with 92% *ee* and 97% *ee*, respectively (see pages S17−S18 of the Supporting Information). The chiral (R_p)-paracyclophane-4-amine was recovered and could be reused.

■ CONCLUSION

DFT calculation and dynamic ^{1}H NMR were carried out to analyze the restricted rotations of specific C−N bond of [2.2]paracyclophane derivative amides and thioamides. A new

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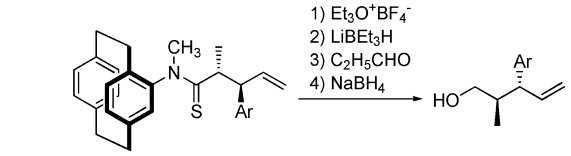
Scheme 6. Removal of the Chiral Auxiliary under Hydrolysis Conditions



chiral thioamide (R_p)-**2d** was screened out based on the theoretical prediction of a rigid side chain caused by forbidden factors in both thermodynamics and kinetics. Distinct chemical surroundings for the *Re* and *Si* faces of the chiral thioamide (R_p)-**2d** could lead to excellent chirality transfer in some asymmetric reactions involving face selectivity. Study of the mechanism revealed that the cisoid pathway should be reasonable during chirality transfer. Here the experiments were prompted by theoretical prediction and resulted in both good yields and excellent diastereoselectivities. As a result, a new methodology for asymmetric synthesis is developed based on theoretical calculation.

COMPUTATIONAL DETAILS

All the initial geometries are taken from XRD structures and optimized at the B3LYP[39](or M06[40])/6-31++G**[41] level. To test the stability of the obtained geometries, analytical frequencies are calculated at each minimum. The dihedral rotation paths are obtained as this procedure: First estimated by flexible scan, in which the interested dihedral angles are scanned at the B3LYP/6-31++G** level, and at each step, all other degrees of freedom (DOF) are optimized. Then the rotation paths are refined by the Synchronous Transit-Guided Quasi-Newton (STQN)[42] method. Each TS is validated using the intrinsic reaction coordinate (IRC)[6] method. Polarizable continuum solvation models (PCM)[43] are performed at each stable point including all the minima and TS. WP04[32]/6-311++G(d,p)/PCM (solvent is set by chloroform or DMSO) and Gauge-Including Atomic Orbital (GIAO)[31] are used to obtain chemical shifts.

EXPERIMENTAL SECTION

(R_p)-(N-Phenyl-N-([2.2]paracyclophan-4-yl)) amide (1a,b,c). To a stirred solution of (R_p)-4-(N-phenylamino)-[2.2]paracyclophane (120 mg, 0.40 mmol) in toluene (2 mL) was added the corresponding acyl chloride. The mixture was heated to 100 °C until the starting material disappeared. After having been cooled to room temperature, ethyl acetate (8 mL) was added to the mixture. The mixture was washed with NaOH aq (2 M, 4 mL × 3) and brine. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using petroleum ether-ethyl acetate (20:1).

For **1a**, 97% yield. Mp 178−179 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 75 °C): δ 7.61−7.53 (m, 4H), 7.42 (t, J = 7.2 Hz, 1H), 6.71 (s, 1H), 6.63−6.58 (m, 2H), 6.45−6.39 (m, 2H), 5.94 (d, J = 7.7 Hz, 1H), 5.59 (br, 1H), 3.33−3.23 (m, 1H), 3.13−3.07 (m, 1H), 3.03−2.85 (m, 6H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 75 °C): δ 169.1, 141.7, 139.3, 138.6, 138.1, 138.0, 136.0, 135.0, 132.5, 131.9, 131.4, 130.4, 128.9, 128.5, 128.1, 126.7, 34.1, 34.1, 33.8, 30.7, 22.5. MS (EI) m/z 341 [M$^+$] (55.91). HRMS (EI) calcd for C24H23NO 341.1780, found 341.1779. IR (cm^{-1}): 1660, 1374, 1334, 698. Anal. Calcd for C25H25NO: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.16; H, 6.83; N, 3.94.

For **1b**, 99% yield. Mp 160−161 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 75 °C): δ 7.61−7.54 (m, 4H), 7.42 (t, J = 7.1 Hz, 1H), 6.70 (s, 1H), 6.62−6.57 (m, 2H), 6.42 (q, J = 7.3 Hz, 2H), 5.92 (d, J = 7.6 Hz, 1H), 5.51 (br, 1H), 3.31−3.25 (m, 1H), 3.13−3.07 (m, 1H), 3.02−2.83 (m, 6H), 1.99−1.89 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 75 °C): δ 172.5, 141.4, 139.4, 138.3, 138.1, 138.1, 136.1, 134.9, 132.5, 131.9, 131.4, 130.4, 129.1, 128.5, 128.3, 126.7, 34.1, 34.0, 33.8, 30.7, 27.1, 8.8. MS (EI) m/z 355 [M$^+$] (36.46). HRMS (EI) calcd for C25H25NO 355.1936, found 355.1934. IR (cm^{-1}): 1666, 1488, 1266, 765, 704. Anal. Calcd for C25H25NO: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.32; H, 7.27; N, 3.76.

For **1c**, 94% yield. Mp 163−164 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$, 75 °C): δ 7.60−7.54 (m, 4H), 7.42 (t, J = 7.0 Hz, 1H), 6.69 (s, 1H), 6.63−6.58 (m, 2H), 6.45−6.39 (m, 2H), 5.93 (d, J = 7.6 Hz, 1H), 5.54 (br, 1H), 3.31−3.22 (m, 1H), 3.13−3.07 (m, 1H), 3.03−2.87 (m, 6H), 1.96−1.90 (m, 2H), 1.45 (dd, J =14.2, 7.1 Hz, 2H), 0.76 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$, 75 °C): δ 171.6, 141.4, 139.3, 138.2, 138.1, 138.0, 136.1, 134.9, 132.5, 132.0, 131.9, 131.4, 130.4, 129.1, 128.5, 128.2, 126.7, 35.6, 34.1, 34.0, 33.8, 30.7, 17.6, 12.9. MS (EI) m/z 369 [M+] (57.37). HRMS (EI) calcd for C26H27NO 369.2093, found 369.2094. IR (cm^{-1}): 1666, 1488, 1368, 1251, 703. Anal. Calcd for C26H27NO: C, 84.51; H, 7.37; N, 3.79. Found: C, 84.48; H, 7.54; N, 3.60.

N-Methyl-N-(R_p)-4-paracyclophane-propionamide 1d. To a stirred solution of (R_p)-paracyclophane-4-methyl amine (450 mg, 1.9 mmol) in CH_2Cl_2 (50 mL) and pyridine (1.5 mL) was added dropwise propionyl chloride (1.25 mL, 14 mmol). After the addition was complete, the mixture was stirred at room temperature overnight. The reaction mixture was quenched with 2 N NaOH (15 mL), and the resulting aqueous layer and EtOAc extracts (15 mL × 2) from the aqueous layer were combined, washed with water, and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using petroleum ether-ethyl acetate (4: 1) to afford 510 mg (92% yield) 4. Mp 170 °C; $[\alpha]^D_{20}$ −172.5 (c 1, $CHCl_3$); IR (cm^{-1}) 2956, 2920, 2851, 1736, 1654, 1419, 1377; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H), 1.72−1.80 (m, 1H), 1.98−2.06 (m,1H), 2.92−3.19 (m, 8H), 3.57 (s, 3H), 6.37−6.46 (m, 4H), 6.57 (d, J = 7.8 Hz, 1H), 6.66−6.73 (m, 2H); IR (cm^{-1}) 1654, 1419, 1377; MS (EI) m/z 293 [M$^+$] (89).

(R_p)-(N-Phenyl-N-([2.2]paracyclophan-4-yl))-propanethioamide (2b). To a stirred solution of (R_p)-**1b** (1.78 g, 50 mmol) in toluene (30 mL) was added Lawesson's reagent. The mixture was refluxed for 30 min and then cooled to room temperature. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using petroleum ester-ethyl acetate-dichloromethane (30:1:2) to afford 1.79 g (96%). Mp 174−177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 4.3 Hz, 4H), 7.51 (qd, J = 8.4, 4.0 Hz, 1H), 6.67−6.45 (m, 5H), 5.78 (d, J = 7.9 Hz, 1H), 4.87 (d, J = 7.9 Hz, 1H), 3.48−2.86 (m, 8H), 2.68−2.54 (m, 0.4H), 2.24 (ddd, J = 14.5, 7.3, 3.8 Hz, 1.5H), 1.27−1.22 (m, 0.7H), 1.05 (t, J =7.3 Hz, 2.3H). (splitting peaks of ethyl group due to rotamer) ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.6, 144.2, 141.4, 139.3, 138.9, 138.4, 136.3, 135.8, 134.3, 132.5, 132.4, 132.2, 132.1, 130.3, 129.6, 128.6, 128.1, 37.2, 34.9, 34.8, 34.5, 31.1, 13.9. MS (EI) m/z 371 [M$^+$] (12.17). HRMS (EI) calcd for C25H25NS 371.1708, found 371.1705. IR (cm^{-1}): 2922, 1593, 1489, 1409, 1387, 1280, 745, 700.

N-Methyl-N-(R_p)-4-paracyclophane-propanethioamide ***2d.*** A mixture of (R_p)-**1d** (500 mg, 1.71 mmol) and Lawesson's reagent (500 mg, 1.19 mmol) was heated in refluxing toluene (10 mL) overnight. The reaction mixture was motioned by TLC. Toluene was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel using petroleum ether-ethyl acetate (6:1) to afford 470 mg (89% yield) 5. Mp 139−140 °C; $[\alpha]_D^{20}$ −492 (c 1, $CHCl_3$); IR (cm^{-1}) 2952, 2927, 1918, 1592, 1473, 1438, 1378, 1313, 1281; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, J = 7.5 Hz, 3H), 2.25−5.34 (m, 2H), 2.85−2.93 (m, 1H), 2.95−3.01 (m, 3H), 3.01−3.21 (m, 4H), 4.04 (s, 3H), 6.37−6.48 (m, 4H), 6.62 (d, J = 7.8 Hz, 1H), 6.71−6.76 (m, 2H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 13.5, 30.9, 34.7, 35.2, 36.7, 45.0, 125.9, 130.7, 131.7, 132.3, 132.9, 134.0, 135.3, 135.5, 139.0, 139.2, 140.8, 141.6, 208.4; IR (cm^{-1}) 1592, 1473, 1438, 1410, 1378; MS (EI) m/z 309 [M$^+$] (62); HRMS (ESI) calcd for $C_{20}H_{24}N_1S_1$ 310.1624, found 310.1624.

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N-Methyl-N-(R_p)-4-paracyclophane-2-methyl-3-phenylpent-4-enethioamide **4a**. This was prepared by the above-mentioned procedure from (R_p)-**2d** and cinnamyl bromide in 91% yield. The NMR spectrum showed two separate signals for CH_2 at δ = 0.83 (B) and 1.19 (A), diastereotopic protons in relation to the paracyclophane plane chirality in a 0.02:3 ratio. Mp 175 °C; IR (cm^{-1}) 3026, 2954, 2928, 2852, 1638, 1594, 1489, 1463, 1373, 1097; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (d, J = 6.3 Hz, 3H), 2.71−2.83 (m, 2H), 2.85−2.98 (m, 3H), 3.00−3.20 (m, 4H), 3.53 (t, J = 9.9 Hz, 1H), 3.62 (s, 3H), 4.88−5.01 (m, 2H), 5.52−5.65 (m, 2H), 6.26 (dd, J = 1.8 and 7.8 Hz, 1H), 6.44−6.50 (m, 3H), 6.64−6.73 (m, 4H), 7.03−7.14 (m, 3H); ^{13}C NMR ($CDCl_3$ 75 MHz): δ 19.8, 31.4, 34.8, 35.1, 35.5, 44.7, 48.3, 58.5, 116.2, 125.9, 127.6, 127.7, 128.0, 130.9, 131.8, 132.3, 133.1, 134.1, 135.3, 135.7, 139.1, 139.2, 139.4, 140.5, 141.7, 142.1; IR (cm^{-1}) 1638, 1594, 1489, 1465, 1435, 1412, 1373, 1301, 1277, 1209; MS (EI) m/z 425 [M^+] (47); HRMS (ESI) calcd for $C_{29}H_{32}N_1S_1$ 426.2249, found 426.2246.

General Procedure for Thio-Claisen Rearrangement Affording N-Methyl-N-(R_p)-4-paracyclophane-2-methylpent-4-enethioamide **4b**. A solution of (R_p)-**2d** (20 mg, 0.065 mmol) in THF (2 mL) was cooled to 0 °C and treated with 2 M LDA (50 μL, 0.098 mmol), and the resulting solution was stirred for 30 min. Allyl bromide (12 mg, 0.098 mmol) was added, and the mixture was stirred for 30 min at 0 °C. It was warm up to RT and refluxed for 6 h. Motioned by TLC, the reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and then diluted with ether. The organic layer was separated, and the aqueous layer was extracted with ether (10 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using petroleum ether-ethyl acetate (20:1) to afford 22 mg (97% yield) 6a. The NMR spectrum showed two separate signals for CH_2 at δ = 0.74 (B) and 1.08 (A), diastereotopic protons in relation to the paracyclophane plane chirality in a 0.14:3 ratio. Mp 198 °C; IR (cm^{-1}) 2958, 2926, 1638, 1591, 1467, 1434, 1409, 1379, 1326, 1092; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (d, J = 6.6 Hz, 3H of B), 1.08 (d, J = 6.6 Hz, 3H of A), 1.84−1.95 (m, 1H), 2.10−2.23, (m, 1H), 2.54−2.66 (m, 1H), 2.79−3.03 (m, 4H), 3.08−3.26 (m, 4H), 4.01 (s, 3H), 4.71 (s, 1H), 4.75 (dd, J = 5.4 Hz, 1H), 5.09−5.24 (m, 1H), 6.33 (d, J = 1.5 Hz, 1H), 6.40 (dd, J = 1.5 and 7.8 Hz, 1H), 6.43−6.52 (m, 2H), 6.62 (dd, J = 1.5 and 7.8 Hz, 1H), 6.68−6.78 (m, 2H); ^{13}C NMR ($CDCl_3$ 75 MHz): δ 20.8, 31.1, 35.0, 35.2, 35.5, 43.0, 43.3, 45.0, 116.0, 126.9, 131.0, 132.5, 133.1, 134.2, 135.7, 135.8, 139.2, 139.5, 141.1, 142.0, 212.6; MS (EI) m/z 349 [M^+] (47); HRMS (MALDI) calcd for $C_{23}H_{28}N_1S_1$ 350.1937, found 350.1940.

N-Methyl-N-(R_p)-4-paracyclophane-2,4-dimethylpent-4-enethioamide **4c**. This was prepared by the above-mentioned procedure from (R_p)-**2d** and methallyl chloride in 91% yield. The NMR spectrum showed two separate signals for CH_2 at δ = 0.74 (B) and 1.08 (A), diastereotopic protons in relation to the paracyclophane plane chirality in a 0.15:3 ratio. Mp 142 °C; IR (cm^{-1}) 2966, 2928, 2854, 1649, 1592, 1467, 1435, 1410, 1376, 1322, 1114, 1088, 1034; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.73 (d, J = 6.9 Hz, 3H of B), 0.99 (s, 3H), 1.07 (d, J = 6.9 Hz, 3H of A), 1.77−1.86 (m, 1H), 2.02−2.12, (m, 1H), 2.73−2.89 (m, 2H), 2.90−3.04 (m, 3H), 3.09−3.25 (m, 4H), 4.02 (s, 3H), 4.42 (s, 1H), 4.47 (s, 1H), 6.34 (s, 1H), 6.40 (dd, J = 1.5 and 7.8 Hz, 1H), 6.48 (s, 2H), 6.62 (dd, J = 1.5 and 7.8 Hz, 1H), 6.68−6.78 (m, 2H); ^{13}C NMR ($CDCl_3$ 75 MHz): δ 20.5, 21.8, 31.1, 35.0, 35.2, 35.5, 41.2, 45.1, 46.8, 111.9, 126.8, 131.0, 131.9, 132.5, 133.1, 134.1, 135.5, 135.9, 139.2, 139.5, 141.2, 141.9, 142.7, 213.0; IR (cm^{-1}) 1649, 1592, 1489, 1467, 1435, 1410, 1376, 1323, 1277; MS (EI) m/z 363 [M^+] (43); HRMS (ESI) calcd for $C_{24}H_{30}N_1S_1$ 364.2093, found 364.2095.

N-Methyl-N-(R_p)-4-paracyclophane-2-methyl-3,3-dimethylpent-4-enethioamide **4d**. This was prepared by the above-mentioned procedure from (R_p)-**2d** and 4-bromide-2-methyl-2-butane in 86% yield. The NMR spectrum could not determinate the ratio of the diastereotopic protons in relation to the paracyclophane plane chirality. 74% *de* is determined by HPLC analysis. Chiral HPLC analysis was performed on a Chiralpak AD-H Analytical Column using hexane:2-propanol = 95:5 as an eluent (0.7 mL/min) detecting at 254 nm. Retention time [min]: $t_{(R\rho, S)}$ = 3.79, $t_{(R\rho, R)}$ = 3.99, $t_{(S\rho, R)}$ = 4.45, $t_{(R\rho, S)}$ = 4.95. Mp 160 °C; IR (cm^{-1}) 2959, 2928, 2854, 1638, 1593, 1489, 1465, 1432, 1411, 1372, 1311; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (s, 3H), 0.79 (s, 3H), 1.08 (d, J = 6.9 Hz, 3H), 2.73−3.04 (m, 5H), 3.08−3.22, (m, 4H), 4.01 (s, 3H), 4.64−4.78 (m, 2H), 5.49−5.60 (m, 1H), 6.34−6.49 (m, 4H), 6.59 (d, J = 7.8 Hz, 1H), 6.67−6.76 (m, 2H); ^{13}C NMR ($CDCl_3$ 75 MHz): δ 16.8, 23.7, 24.9, 31.1, 35.0, 35.3, 35.5, 41.0, 45.6, 50.3, 110.9, 127.2, 131.1, 132.0, 132.4, 133.1, 134.0, 135.5, 136.2, 139.3, 139.4, 141.0, 143.0, 146.4, 210.8; IR (cm^{-1}) 1638, 1593, 1489, 1465, 1432, 1411, 1372, 1360, 1332, 1311; MS (EI) m/z 377 [M^+] (24); HRMS (ESI) calcd for $C_{25}H_{32}N_1S_1$ 378.2250, found 378.2252.

N-Methyl-N-(R_p)-4-paracyclophane-2,3-dimethylpent-4-enethioamide **4e**. This was prepared by the above-mentioned procedure from (R_p)-**2d** and crotyl bromide in 74% yield. The NMR spectrum and Chiral HPLC analysis could not determine the ratio of the diastereotopic protons in relation to the paracyclophane plane chirality. Mp 115 °C; IR (cm^{-1}) 2953, 2925, 2853, 1643, 1593, 1467, 1436, 1410, 1376; ^{1}H NMR (300 MHz, $CDCl_3$):δ 0.51 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.0 Hz, 3H), 2.17−2.46 (m, 2H), 2.76−3.02 (m, 4H), 3.08−3.22 (m, 4H), 4.06 (s, 3H), 4.77−4.90 (m, 2H), 5.12−5.25 (m, 1H), 6.28−6.51 (m, 4H), 6.57−6.64 (m, 1H), 6.69−6.77 (m, 2H); ^{13}C NMR ($CDCl_3$ 75 MHz): δ 16.9, 18.3, 18.7, 20.0, 31.2, 35.0, 35.2, 35.6, 45.0, 46.8, 48.4, 114.7, 126.8, 127.2, 131.0, 132.0, 132.5, 133.2, 134.2, 135.6, 135.7, 135.9, 139.2, 139.5, 141.2, 142.0, 212.9; IR (cm^{-1}) 1643, 1593, 1489, 1467, 1436, 1410, 1376; MS (EI) m/z 363 [M^+] (47); HRMS (ESI) calcd for $C_{24}H_{30}N_1S_1$ 364.2093, found 364.2091.

N-Methyl-N-(R_p)-4-paracyclophane-2-methyl-3-(4-nitrophenyl)-pent-4-enethioamide **4f**. This was prepared by the above-mentioned procedure from (R_p)-**2d** and 4-nitro-cinnamyl bromide in 87% yield. The NMR spectrum showed two separate signals for CH_2 at δ = 0.94 (B) and 1.20 (A), diastereotopic protons in relation to the paracyclophane plane chirality in a 0.07:3.09 ratio. Mp 209 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, J = 6.48 Hz, 3H), 2.73−3.21 (m, 10H), 3.63 (s, 3H), 4.93−5.03 (m, 2H), 5.46−5.59 (m, 2H), 6.26 (dd, J = 8.0 and 1.6 Hz, 1H), 6.46−6.53 (m, 3H), 6.69 (ddd, J = 17.6 Hz, 7.8 Hz and 1.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 1H), 7.9 (d, J = 8.76 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.9, 31.4, 34.7, 35.1, 35.5, 44.7, 48.0, 58.1, 117.7, 122.9, 127.0, 128.9, 130.8, 131.8, 132.4, 133.1, 134.3, 135.6, 135.9, 137.7, 138.9, 139.4, 141.1, 141.4, 146.1, 150.1, 209.7; IR (cm^{-1}) 1639, 1605, 1595, 1518, 1467, 1437, 1412, 1377, 1345, 1099, 918, 846; MS (EI) m/z 470.2 [M^+]; HRMS (EI) calcd. for $C_{29}H_{30}N_2O_2S$ 470.2028, found 470.2019.

N-Methyl-N-(R_p)-4-paracyclophane-2-methyl-3-(2,4-dichlorophenyl)pent-4-enethioamide **4g**. This was prepared by the above-mentioned procedure from (R_p)-**2d** and 2,4-dichloro-cinnamyl bromide in 74% yield. The NMR spectrum showed two separate signals for CH_2 at δ = 1.00 (B) and 1.22 (A), diastereotopic protons in relation to the paracyclophane plane chirality in a 0.02:3 ratio. Mp 185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, J = 6.4 Hz, 3H), 2.78−3.26 (m, 10H), 3.72 (s, 3H), 4.20 (t, J = 9.8 Hz, 1H), 4.89 (dd, J = 10.0 and 1.5 Hz, 1H), 5.01 (d, J = 16.9 Hz, 1H,), 5.35−5.47 (m, 1H), 6.06 (s, 1H), 6.28−6.35 (m, 2H), 6.49−6.56 (m, 3H), 6.73 (ddd, J = 18.9 Hz, 7.8 and 1.6 Hz, 2H), 6.93 (dd, J = 8.3 and 2.1 Hz, 1H), 7.22 (d, J = 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.1, 31.7, 34.9, 35.2, 35.6, 45.0, 46.2, 54.1, 117.2, 126.2, 127.3, 129.4, 129.6, 130.9, 131.8, 132.4, 133.2, 134.4, 135.0, 135.8, 136.1, 137.7, 138.5, 139.0, 139.4, 141.0, 141.7, 142.2, 210.5; IR (cm^{-1}) 1635, 1586, 1559, 1470, 1430, 1371, 1344, 1263, 1084, 1048, 817; MS (EI) m/z 493 [M^+]; HRMS (EI) calcd. for $C_{29}H_{29}NCl_2S$ 493.1398, found 493.1404.

Conversion of **4a** *into (2R, 3R)-2-Methyl-3-phenyl-4-penten-l-ol* **5a**. Thioamide **4a** (138 mg, 0.32 mmol) was dissolved in dry 2 mL of CH_2C1_2 and treated with Meerwein's reagent $Et_3O^+BF_4^-$ (0.78 mL, 0.78 mmol, 1 M solution in CH_2Cl_2). The resulting solution was heated to gentle reflux for 2 h in an oil bath. The solvent was removed in vacuo, and the residue was dissolved in dry THF (2 mL). This solution was added dropwise into a solution of $LiBEt_3H$ (0.81 mL, 1 M solution in THF) in dry THF (2 mL) at −78 °C. The resulting suspension was stirred at −78 °C for 1 h. Neat C_2H_5CHO (94 mg,

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1.62 mmol) was added, and the reaction mixture was warmed up to room temperature in 30 min. The reaction mixture was then cooled to −78 °C and saturated aqueous $NaHCO_3$ (4 mL) was added, and the reaction mixture was warmed to room temperature, extraction with ether (5 mL × 4). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo at room temperature. The residue was dissolved in 8 mL of MeOH and cooled to 0 °C followed by addition of solid $NaBH_4$ (122 mg, 3.2 mmol). The suspension was stirred for 20 min and quenched by dropwise addition of water. The reaction mixture was acidified with 2 N HC1 and extracted with ether (5 mL × 4). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and flash chromatography on silica gel using petroleum ether-ethyl acetate (15: 1) to afford (2*R*, 3*R*)-2-methyl-3-phenyl-4-penten-l-ol (24 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, J = 6.8 Hz, 3H), 2.02 (td, J = 13.3 and 6.5 Hz, 1H), 3.22 (t, J = 9.0 Hz, 1H), 3.32 (dd, J = 10.7 and 6.0 Hz, 1H), 3.47 (dd, J = 10.8 and 4.9 Hz, 1H), 5.07 (s, 1H), 5.11 (d, J = 5.3 Hz, 1H), 5.96−6.08 (m, 1H), 7.19−7.22 (m, 3H), 7.30 (q, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 40.2, 53.0, 66.3, 115.9, 126.3, 127.7, 128.6, 139.7, 143.5; MS (EI) m/z 176 [M^+] (6.57). By comparison of literature's ^{1}H NMR, the (2*R*, 3*R*)-2-methyl-3-phenyl-4-penten l-ol were determined in 98% *de* and 92% *ee* (^{1}H NMR of the Mosher ester).

Conversion of ***4f*** *into (2R, 3R)-2-Methyl-3-(4-nitrophenyl)-4-penten-l-ol* ***5f***. (2*R*, 3*R*)-2-Methyl-3-(4-nitrophenyl)-4-penten-l-ol was prepared by the above-mentioned procedure from **4f** in 57% yield with 97% *ee* (^{1}H NMR of the Mosher ester). $[\alpha]_D^{25}$ 87.2 (c 0.69, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (d, J = 6.8 Hz, 3H), 2.04 (td, J = 13.3, 6.5 Hz, 1H), 3.29−3.35 (m, 1H), 3.42−3.49 (m, 2H), 5.14 (d, J = 16.9 Hz, 1H), 5.17 (d, J = 9.3 Hz, 1H), 5.99 (td, J = 16.8 and 9.8 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 8.17 (d, J = 8.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 40.2, 52.2, 65.6, 117.6, 123.8, 128. 6, 137.7, 151.6; IR (cm^{-1}): 3378, 2965, 1603, 1519, 1110, 1032, 921, 858, 707. MS (EI) m/z 221 [M^+] (1.60). HRMS (EI) calcd. for $C_{12}H_{15}NO_3$ 221.1052, found 221.1056.

■ ASSOCIATED CONTENT

Supporting Information

CIF files and additional details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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