Electronic Supplementary Information

Elucidation of the Atroposelectivity in the Synthesis of Axially Chiral Thiohydantoin Derivatives

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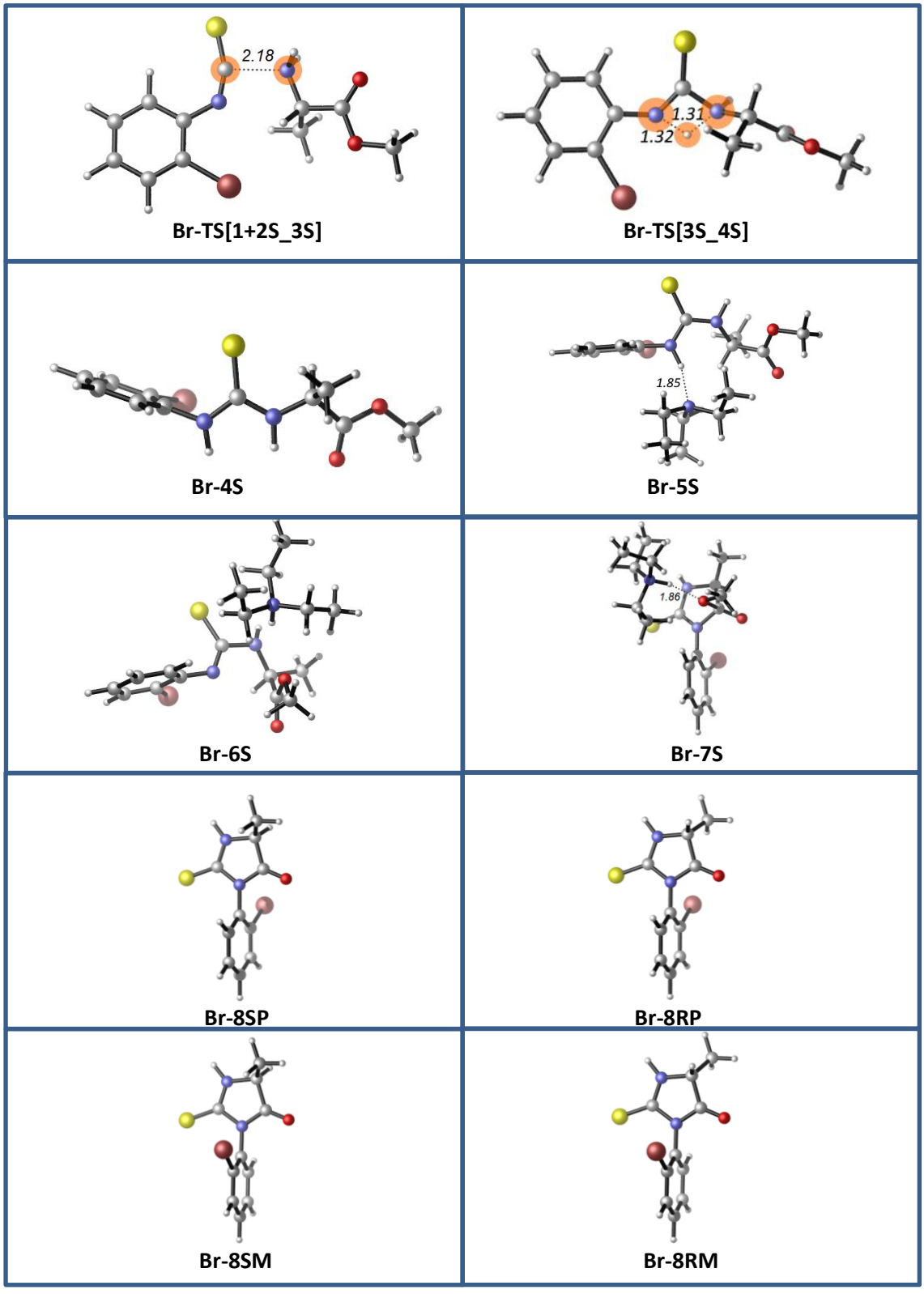
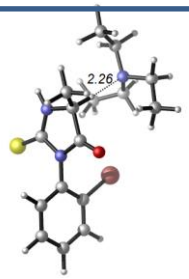
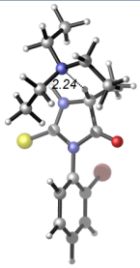
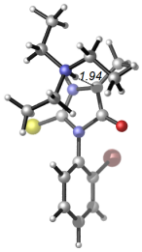
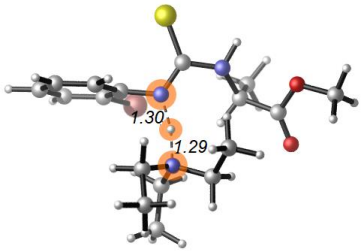
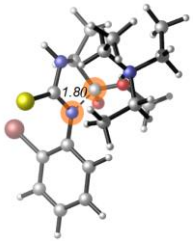
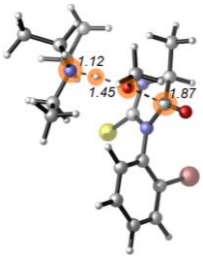
Content

1. 3D Representations of Structures

Fig. S1 3D representations of intermediate, complex and transition state structures for X:Br.



 **Br-9SP**	 **Br-9RP**
 **Br-10**	 **Br-TS[5S_6S]**
 **Br-TS[6S_7S]**	 **Br-TS[7S_8SP]**

2. Can Racemization Occur Before Cyclization?

i. Reactions of 3*S*

The intermediate **3*S*** either cyclizes via **TS[3*S*_8*S*]** to give **8*S*** or undergoes racemization via **TS[3*S*_13]** without any assistance or **TS[11*S*_12]** with the assistance of TEA, or through keto-enol tautomerization via **TS[3*S*_3-*Enol*]** and then cyclizes to **8*R*** (Fig. S2). Relative Gibbs free energies of the intermediates and transition states with respect to structure **3*S*** are given in italics (kcal/mol).

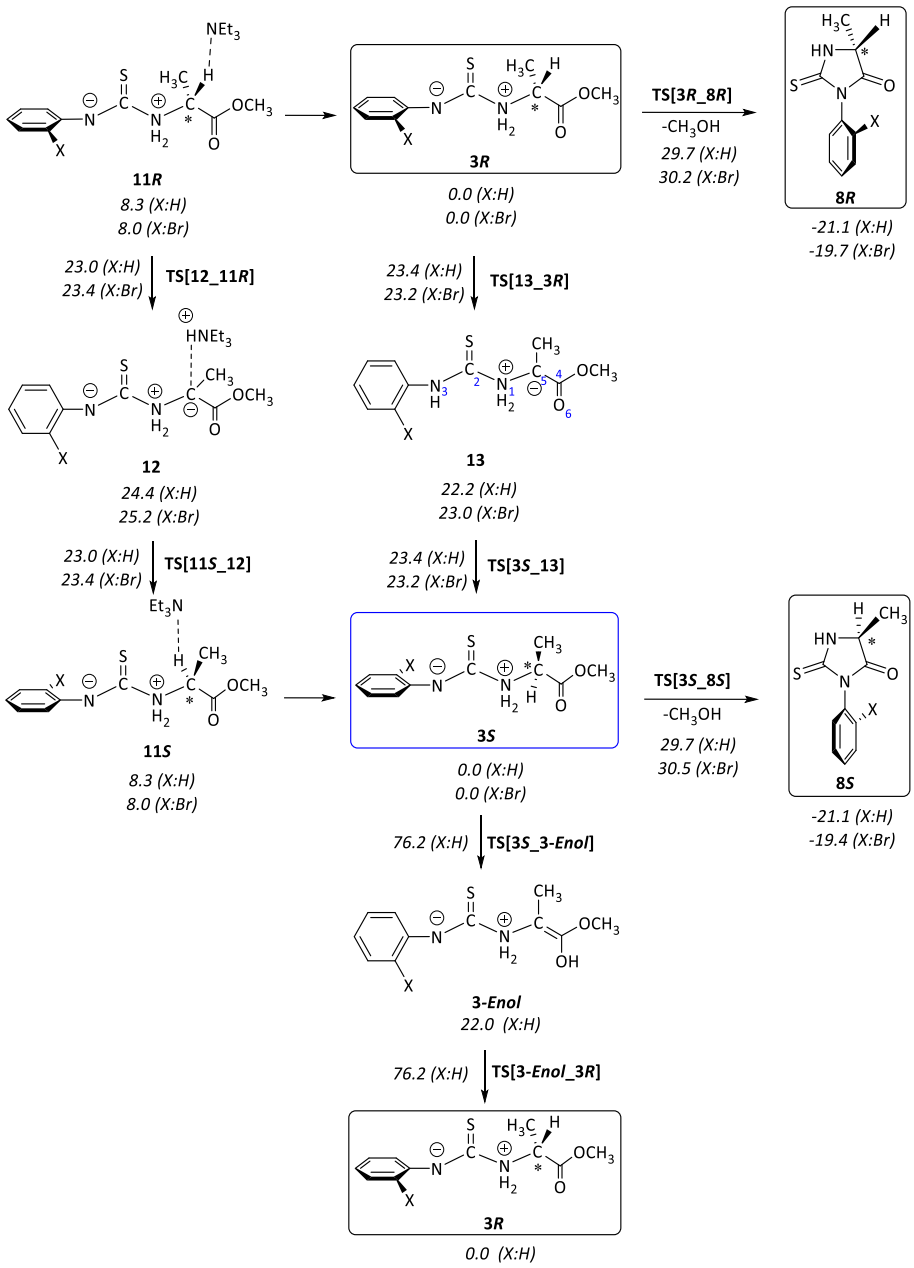


Fig. S2 Alternative cyclization and racemization routes of **3*S*** with and without the assistance of TEA.

The activation barriers for proton migration from the stereocenter (C_5) to the negatively charged arylamine nitrogen (N_3) via **TS[3*S*_13]** are 23.4 and 23.2 kcal/mol for compounds **H** and **Br** respectively giving the intermediate **13** (Fig. S3). Following the free rotation about the N_1-C_5 bond in intermediate **13,** the arylamine nitrogen N_3 transfers the proton back to the sp^2 carbon (C_5) (**TS[13_3*R*]**) to give the enantiomer

3*R*. The racemization of **3*S*** may be achieved with the assistance of TEA through **TS[11*S*_12]** (Fig. S4). **3*S*** and TEA form the complex **11*S***, and this complex is 8.3 kcal/mol and 8.0 kcal/mol higher in energy as compared to the uncomplexed ligands for **H-11*S*** and **Br-11*S*** respectively due to the steric effects caused by TEA as it approaches to form the respective complexes. The complexation to **H-11*S*** and hydrogen abstraction in **H-TS[11*S*_12]** has a barrier of 23.0 kcal/mol, the formation of complex **Br-11*S*** and **Br-TS[11*S*_12]** requires 23.4 kcal/mol. The electron delocalization is weaker in intermediate **12**, and this leads to a relatively unstable structure which lies slightly higher in energy with respect to the transition state structures. After the proton transfer from the protonated TEA to the intermediate **12** via **TS[12_11*R*]**, **11*R*** is formed as a complex of TEA. The isolated uncomplexed racemized product **3*R*** further cyclizes to give **8*R***. The enol tautomer of **3*S*** can be generated via the transfer of the C_5 proton to O_6. In dichloromethane, the relative energy of the enol tautomer (**H-3-*Enol***) is found to be 22.0 kcal/mol higher with respect to the keto isomer (**H-3*S***) (Fig. S5), and its formation requires 76.2 kcal/mol indicating the presence of the keto isomer in the reaction medium only.

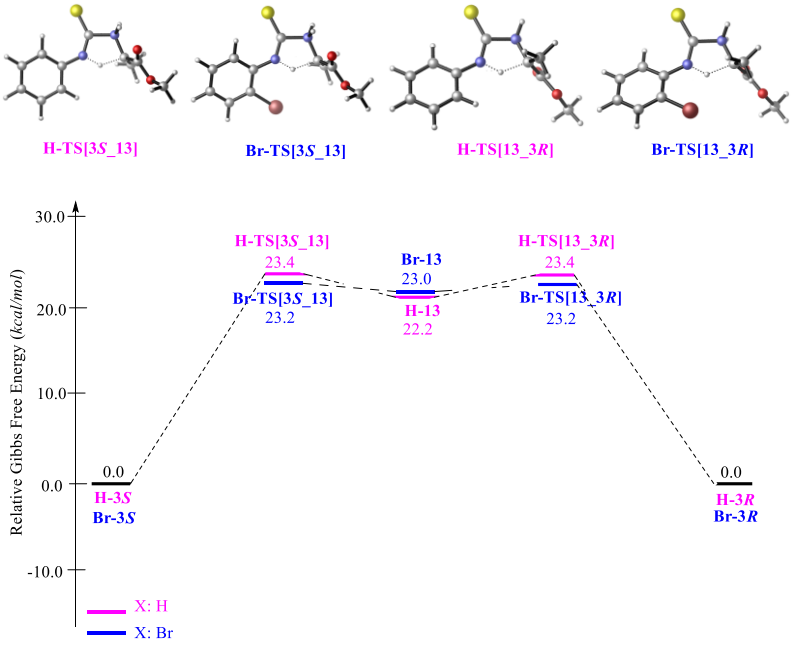


Fig. S3 Free energy profile for unassisted **3*S*** → **3*R*** transformation.

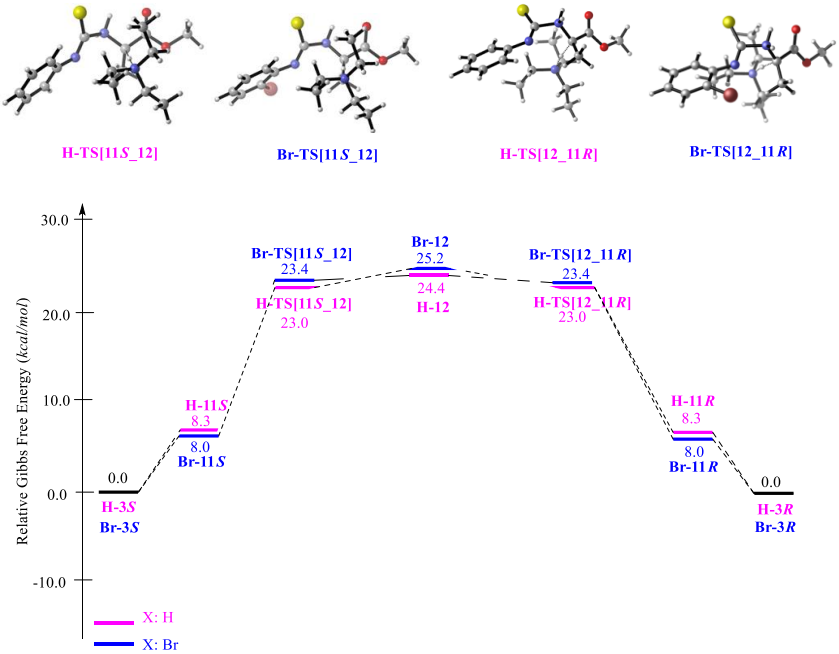


Fig. S4 Free energy profile for **3*S*** → **3*R*** transformation with the help of TEA.

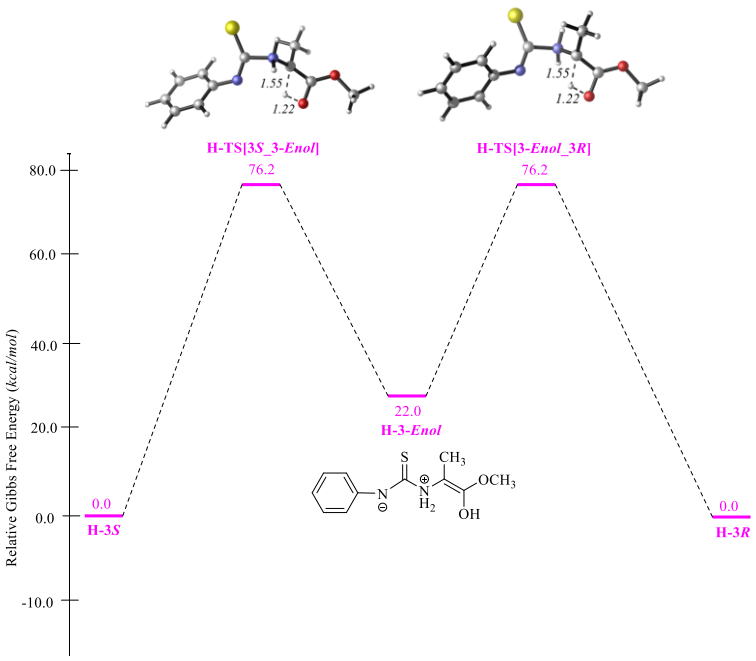


Fig. S5 Free energy profile for the racemization of **H-3*S*** via keto-enol tautomerization.

The two potential energy surfaces displayed in Fig. S3 and Fig. S4 indicate the formation of racemic mixtures for both **H-3** and **Br-3**, since the barriers for the reverse and forward reactions are equal. In **Br-3*R*-1**, the bromine atom is in antiperiplanar conformation with respect to methyl group attached to C_5 and **Br-3*R*-1** is 2.9 kcal/mol more stable than **Br-3*R*-2** (Br atom in synperiplanar conformation) (Fig. S6) due to the similar favorable interactions as observed in **Br-3*S*-1**. Thus, upon the cyclization of **Br-3*R*-1**, the **Br-8*R*M** atropoisomer is expected to be formed.

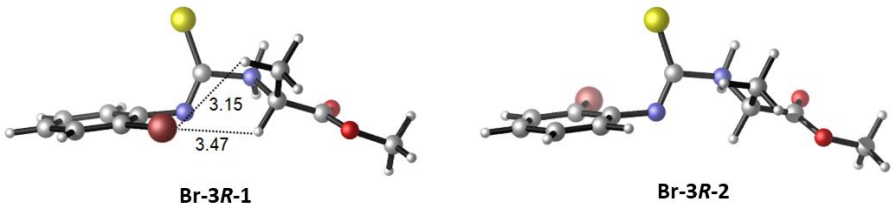


Fig. S6 3D representations and geometric parameters for **Br-3*R*-1 and Br-3*R*-2.**

3*S* and **3*R*** can undergo cyclization via a concerted reaction mechanism: Following some conformational reorganizations, the nucleophilic attack of electron rich nitrogen atom (N_3) to the carbonyl carbon (C_4) (**TS[3_8]**) initiates the ring closure simultaneously promoting the hydrogen movement from the amidic nitrogen (N_1) to the methoxy oxygen, yielding the thiohydantoin ring (**8**) and methyl alcohol. This ring-closure transition state embodies a *5-endo-trig* nucleophilic cyclization which has been considered as a geometrically disfavored process according to Baldwin's rules.[1-4] There are a number of *5-endo-trig* cyclizations which are reported in the recent literature.[3] In the case of cyclization of **3**, there are no steric or electrostatic repulsions between N_3 and C_4. The carboxyl oxygen readily abstracts the hydrogen from N_1 and releases methanol as the ring closes. This concerted cyclization reaction requires 29.7 kcal/mol for the formation of the racemic **H-8**, 30.5 kcal/mol for **Br-8*S*P** and 30.2 kcal/mol for **Br-8*R*M** (Fig. S7). Despite the relatively high activation barrier (compared to racemization of **3** or conversion of **3*S*** to **4*S***) needed for cyclization of **3**, there is a tremendous gain in thermodynamic stability in reaching the cyclized products; and this suggests a thermodynamically driven process. The exergonic character of this step can be attributed to the delocalization gained in the cyclic products.

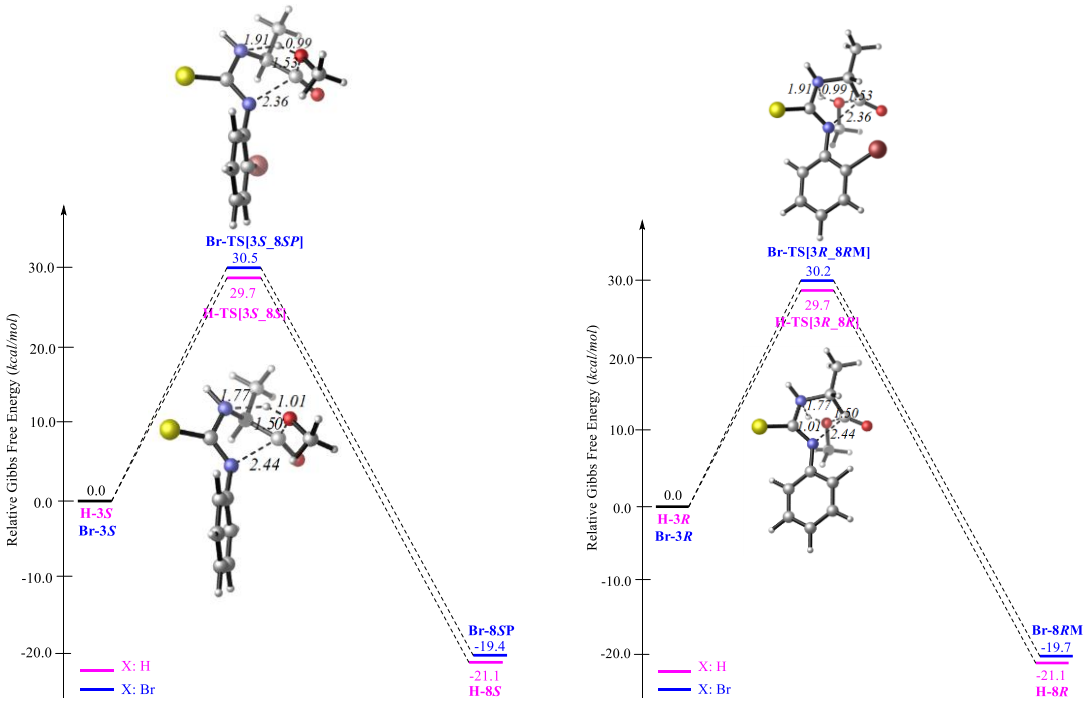


Fig. S7 Free energy profile for cyclization from **3*S*** (left) and **3*R*** (right)

ii. Reactions of* 4*S

The intermediate **4*S*** may either cyclize through **TS[4*S*_8*S*]** to give **8*S*** or is assisted by TEA, it may enantiomerize via **TS[14*S*_15]** or through keto-enol tautomerization via **TS[4*S*_4-Enol]** and then cyclize to **8*R*** (Fig. S8).

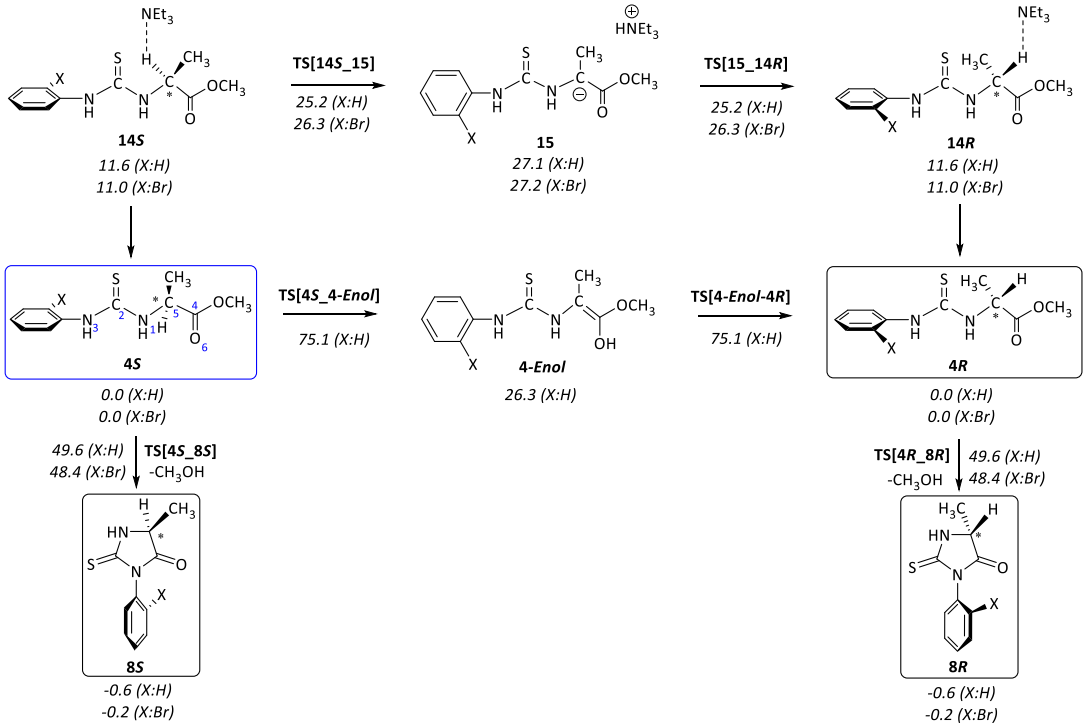


Fig. S8 Alternative cyclization and racemization routes of **4*S*** with and without the assistance of TEA.

TEA can form the complex **14*S*** by interacting with the hydrogen atom of the stereocenter. The complexation to **H-14*S*** and hydrogen abstraction in **H-TS[14*S*_15]** overcomes a barrier of 25.3 kcal/mol, while the same barrier is 26.3 kcal/mol for **Br-14*S*** and **Br-TS[14*S*_15]** (Fig. S9). In **TS[15_14*R*]** the protonated TEA transfers the proton to the sp^2 carbon (C_5) from the *Re* face of **15** to give the **14*R***. The potential energy surface (PES) in Fig. S9 indicate the formation of racemic mixtures for both **H-4** and **Br-4**, since reaching the summit of the PES requires equal energies in both forward and reverse reactions which is in agreement with experimental data for the formation of **H-8** but does not satisfy the expectation for **Br-8** for which the ***S*** isomer is dominant experimentally.

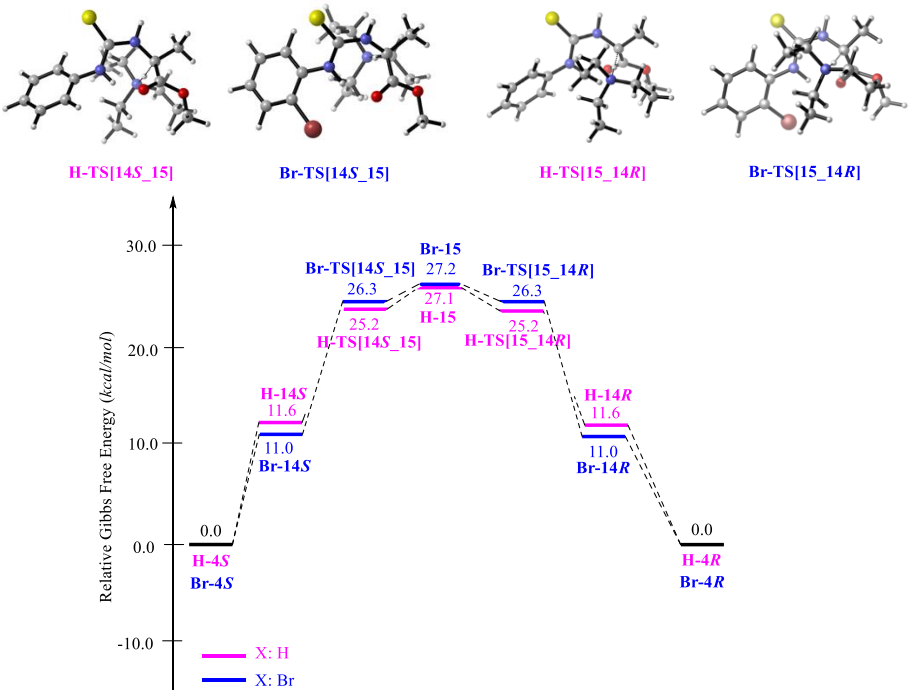


Fig. S9 Free energy profile for **4*S*** → **4*R*** transformation

On the other hand, **4*S*** can undergo keto-enol tautomerization by the transfer of C_5 proton to O_6. The calculated barrier is 75.1 kcal/mol and the relative energy of the enol tautomer (**H-4-*Enol***) is found to be 26.3 kcal/mol higher with respect to the keto isomer **H-4*S***, indicating the presence of the keto isomer in the reaction medium only (Fig. S10).

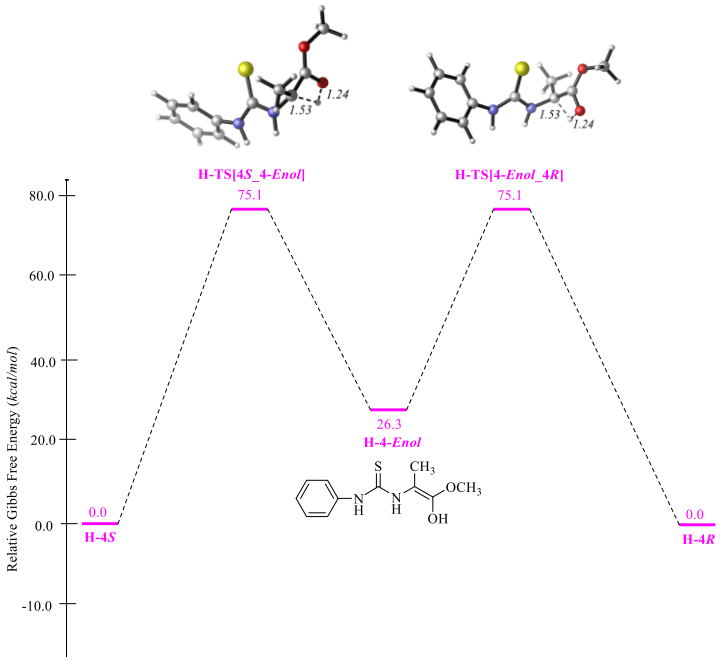


Fig. S10 Free energy profile for the racemization of **H-4*S*** via keto-enol tautomerization

Structure **4** can undergo a concerted ring closure via the simultaneous hydrogen transfer from arylamine nitrogen (N_3) to the methoxy oxygen to release methyl alcohol with the attack of N_3 to C_4. The transition state structure corresponding to the cyclization of **4*S*** resembles the product; the activation barriers for this cyclization step are 49.6 kcal/mol for the formation of racemic mixture of **H-8**, 48.4 kcal/mol for **Br-8*S*P** and 48.4 kcal/mol for **Br-8*R*M**. These barriers are not attainable under the reaction conditions (Fig. S11).

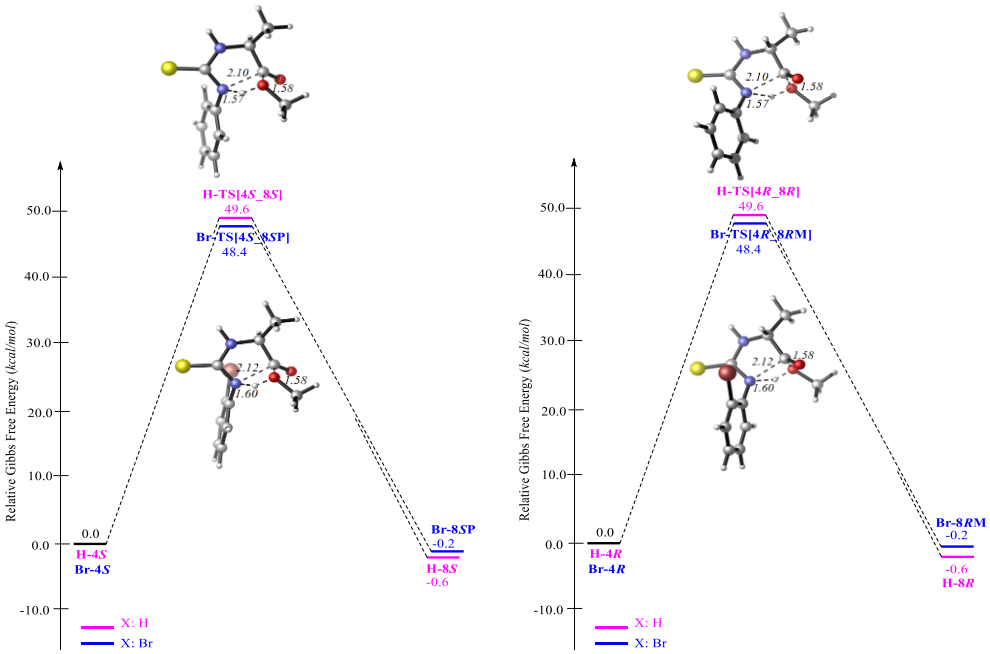


Fig. S11 Free energy profile for cyclization from **4*S*** (left) and **4*R*** (right).

iii. Reactions of 6*S*

The intermediate **6*S*** either cyclizes to **8*S*** in two-steps with the assistance of TEA as discussed in cyclization part or follows an independent enantiomerization via **TS[6*S*_16]**, and then yields **8*R*** by cyclization (Fig. S12).

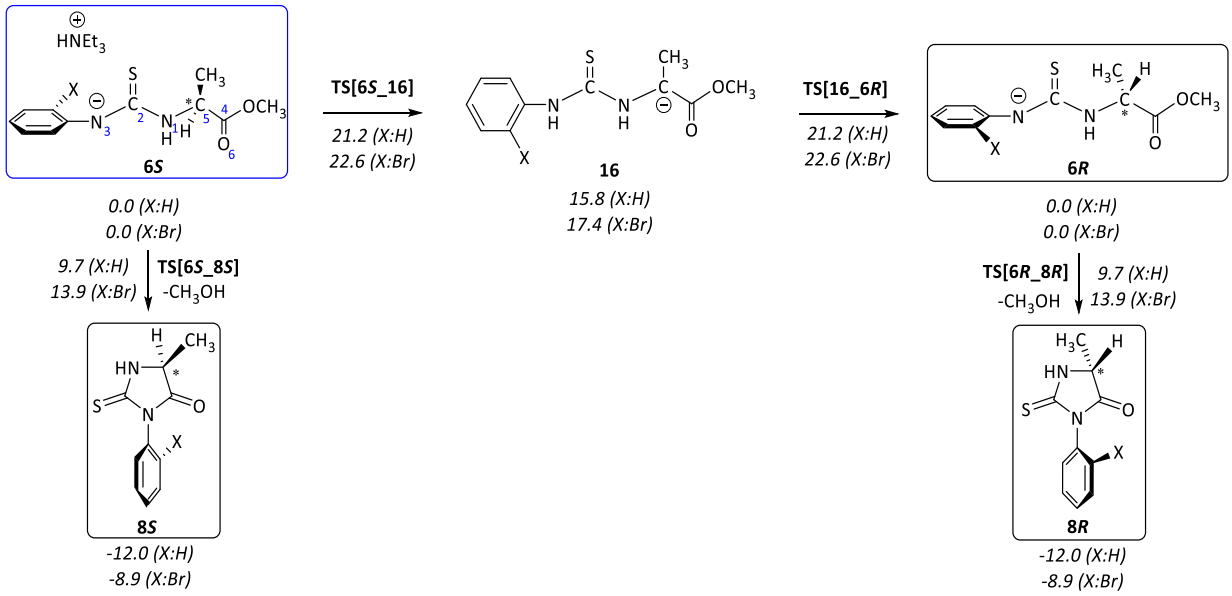


Fig. S12 Alternative racemization route of **6*S***.

The electron rich N_3 abstracts the hydrogen atom from the stereocenter via **TS[6*S*_16]** with activation barriers of 21.2 kcal/mol for **H** and 22.6 kcal/mol for **Br**. After the free rotation about the N_1-C_5 bond in **H-16** and **Br-16**, hydrogen at N_3 is transferred back to the sp^2 C_5 to give **H-6*R*** and **Br-6*R***. The potential energy surface in Fig. S13 indicates the formation of racemic mixtures for both **H-6** and **Br-6**; the barriers for the reverse and forward reactions are the same. Moreover, as in the case of **Br-3*R*** and **Br-4*R***, the bromine arranges itself in the antiperiplanar conformation with respect to C_5 methyl, indicating that the **M** atropoisomer should be dominant in the final cyclized **Br-8*R*** product. Favorable interactions between Br and H atoms render **Br-6*R*** 1.8 kcal/mol more stable than its other conformer **Br-6*R*-2** in which bromine is in synperiplanar conformation (Fig. S14).

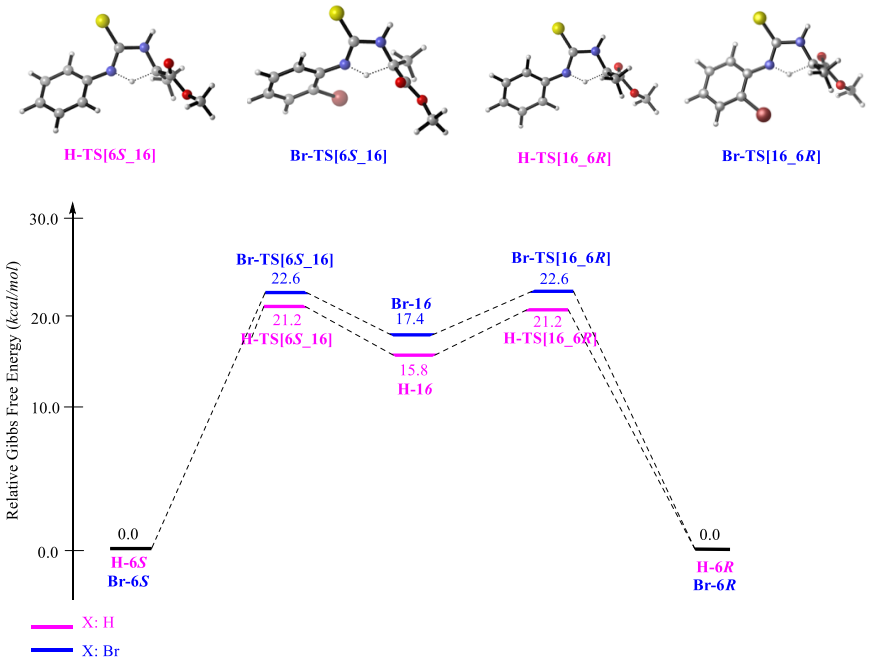


Fig. S13 Free energy profile for **6*S*** → **6*R*** transformation.

Even though the racemization barrier of **6*S*** is reachable under reaction conditions, **6*S*** to **8*S*** transformation is highly favored due to much lower barrier.

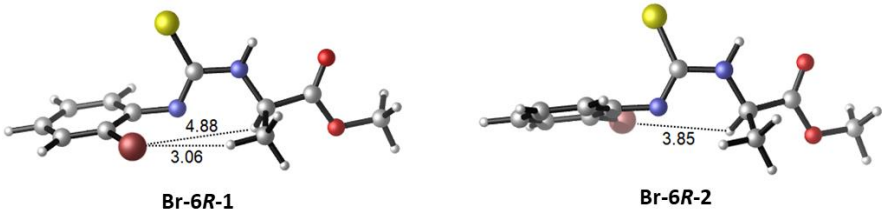


Fig. S14 3D representations and geometric parameters for **Br-6*R*-1 and Br-6*R*-2.**

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1. J.E. Baldwin, *J. Chem. Soc. Chem. Commun*., 1976, 734-736.
2. J.E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R.C. Thomas, *J. Chem. Soc. Chem. Commun.*, 1976, 736-738.
3. J.E. Baldwin, R.C. Thomas, L. Kruse and L. Silberman, *J. Org. Chem.*, 1977, **42**, 3846-3852.
4. C. Chatgilialoglu, C. Ferreri, M. Guerra, V. Timokhin, G. Froudakis and T. Gimisis, *J. Am. Chem. Soc.*, 2002, **124**, 10765-10772.