

Computational modeling

Initial geometries for the oxygen atom transfer reaction were obtained by manual embedding using the Avogadro GUI¹. Optimization at the GFN2-XTB²/ALPB(CHCl₃)³ level via XTB, followed by refinement at the R²SCAN-3c⁴/CPCM(CHCl₃)⁵ level via ORCA⁶ 5.0.4 gave two initial transition state geometries for the reaction. From these, constrained metadynamics-based conformational searches were performed with CREST⁷ at the GFN2-XTB/ALPB(CHCl₃)/GFN-FF/ALPB(CHCl₃) level via TSCoDe⁸ 0.4.16. The resulting conformational ensembles were refined within TSCoDe at the GFN2-xTB/ALPB(CHCl₃) level (RMSD threshold = 0.5 Å, energy window = 10 kcal/mol). The constrained conformational search and refinement protocol was repeated a total of three times with different constraints to ensure complete characterization of the transition state conformational space. Initially, just the O-O distance of the breaking bond on the peracid and the S-O distance of the incipient sulfoxide bond were constrained to 1.65 and 2.45 Å, respectively, as fixed TSCoDe constraints (uppercase letters). The second and third run were added the N-H distance constraint of the catalyst β -turn hydrogen bond only during conformational search (lowercase letter). These searches were agnostic with respect to sulfur absolute configuration and generated transition state-like conformers leading to both enantiomers of the sulfoxide product.

The refined TSCoDe ensembles were pooled and pruned again for similarity with TSCoDe (RMSD threshold = 0.5 Å). The structures were then relaxed at the R²SCAN-3c/CPCM(CHCl₃) level via ORCA with a distance constraint on the incipient sulfoxide S-O bond set to 2.45 Å, and successively optimized to the closest first order saddle point at the same level. Both constrained optimization and saddle point optimization used the Defgrid3 and TightOpt keywords, with a %geom MaxStep of 0.05 bohrs. Vibrational analysis was carried out at the same level of theory (4 °C, 277.15 K) and the transition state nature was ascertained by the presence of a single imaginary mode involving the motion of the transferred oxygen atom and by IRC calculation endpoints being consistent with reagents and products for the desired chemical reaction.

Transition states within 3 kcal/mol from the most stable ($\Delta G_{R^2SCAN-3c/CPCM(CHCl_3)}$) were subjected to a single point energy calculation at the ω B97M-V⁹/def2-TZVPP¹⁰/SMD¹¹(CHCl₃) level. The final relative free energy of each structure was composed from the high-level single point electronic energy and the lower-level free energy correction, and is referred to as ω B97M-V/def2-TZVPP/SMD(CHCl₃)/R²SCAN-3c/CPCM(CHCl₃) (**Table 1**). The free energy difference between the lowest energy transition state for each enantiomer of the product is 1.52 kcal/mol at this level, which reflects a predicted selectivity of 94:6 er, in exact agreement with the observed value of 94:6 er.

energy	EE - ω B97M-V/def2-TZVPP/SMD(CHCl ₃)	G _{corr} - R ² SCAN-3c/CPCM(CHCl ₃), 277 K	composite G	$\Delta\Delta G^\ddagger$
unit	Eh	Eh	Eh	kcal/mol
pro-R	-4718.803587	0.96844829	-4717.835139	0.00
pro-S	-4718.801580	0.96886337	-4717.832716	1.52

Table 1. Final energies for the best conformers of the major (pro-*R*) and minor (pro-*S*) transition states.

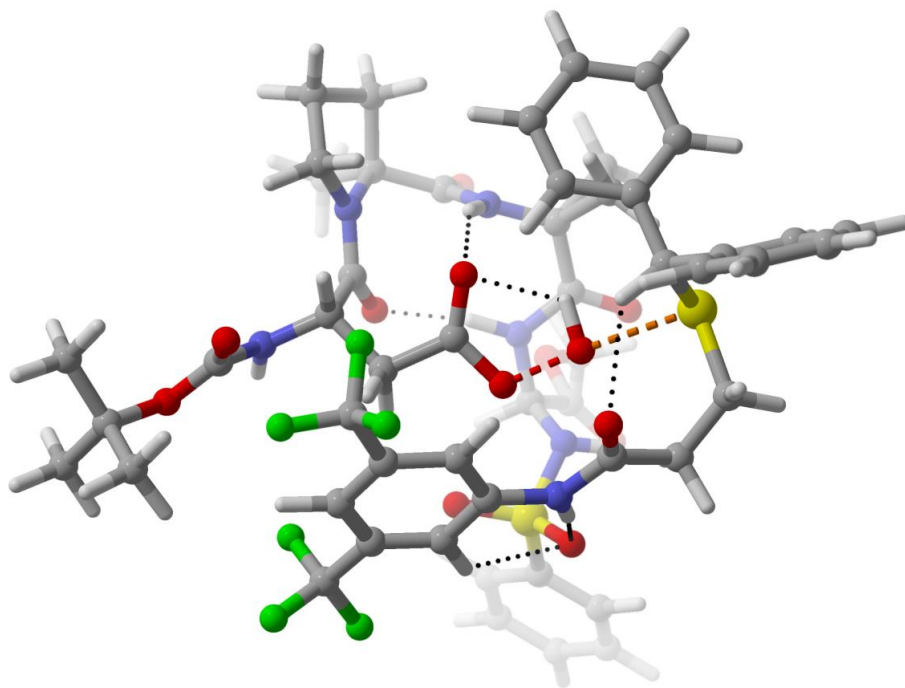


Figure 1. Lowest energy *pro-R* transition state, leading to the observed major product.

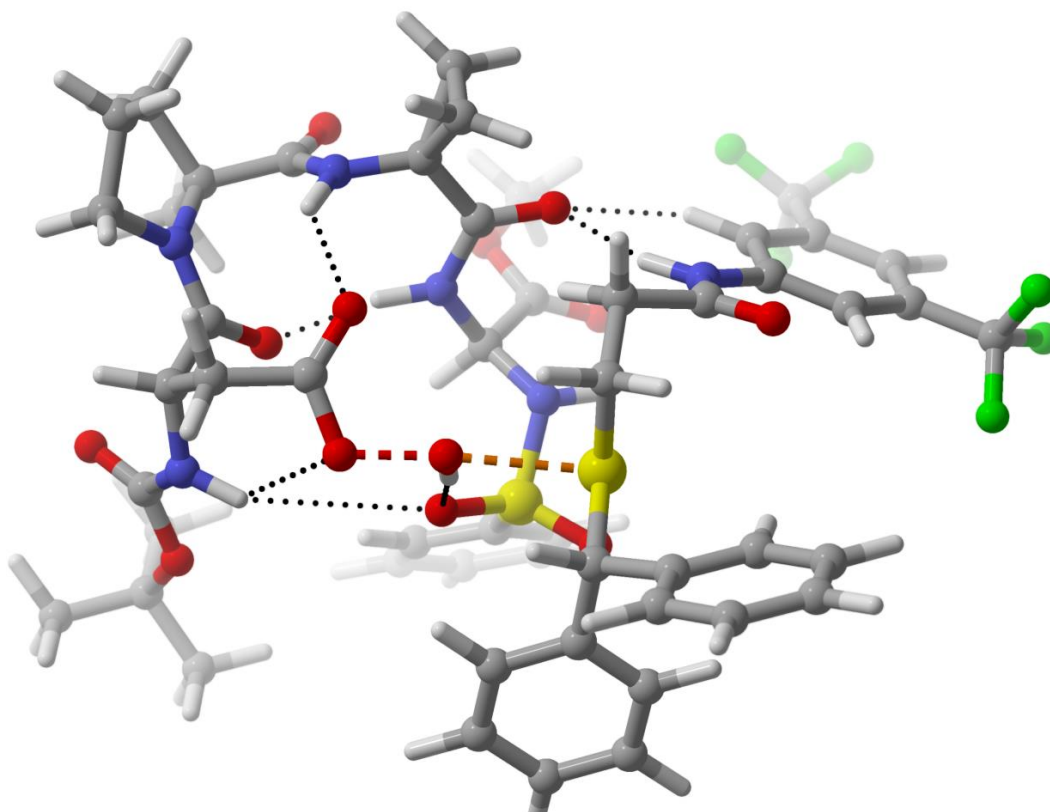


Figure 2. Lowest energy *pro-S* transition state, leading to the observed minor product.

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