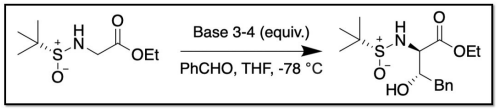
# A Computational Investigation Into the Diastereoselectivity of Auxiliary-directed Aldol Reactions

Alex Orebic and Jefferey Cannon
Occidental College, Department of Chemistry, Los Angeles, California

aorebic@oxy.edu

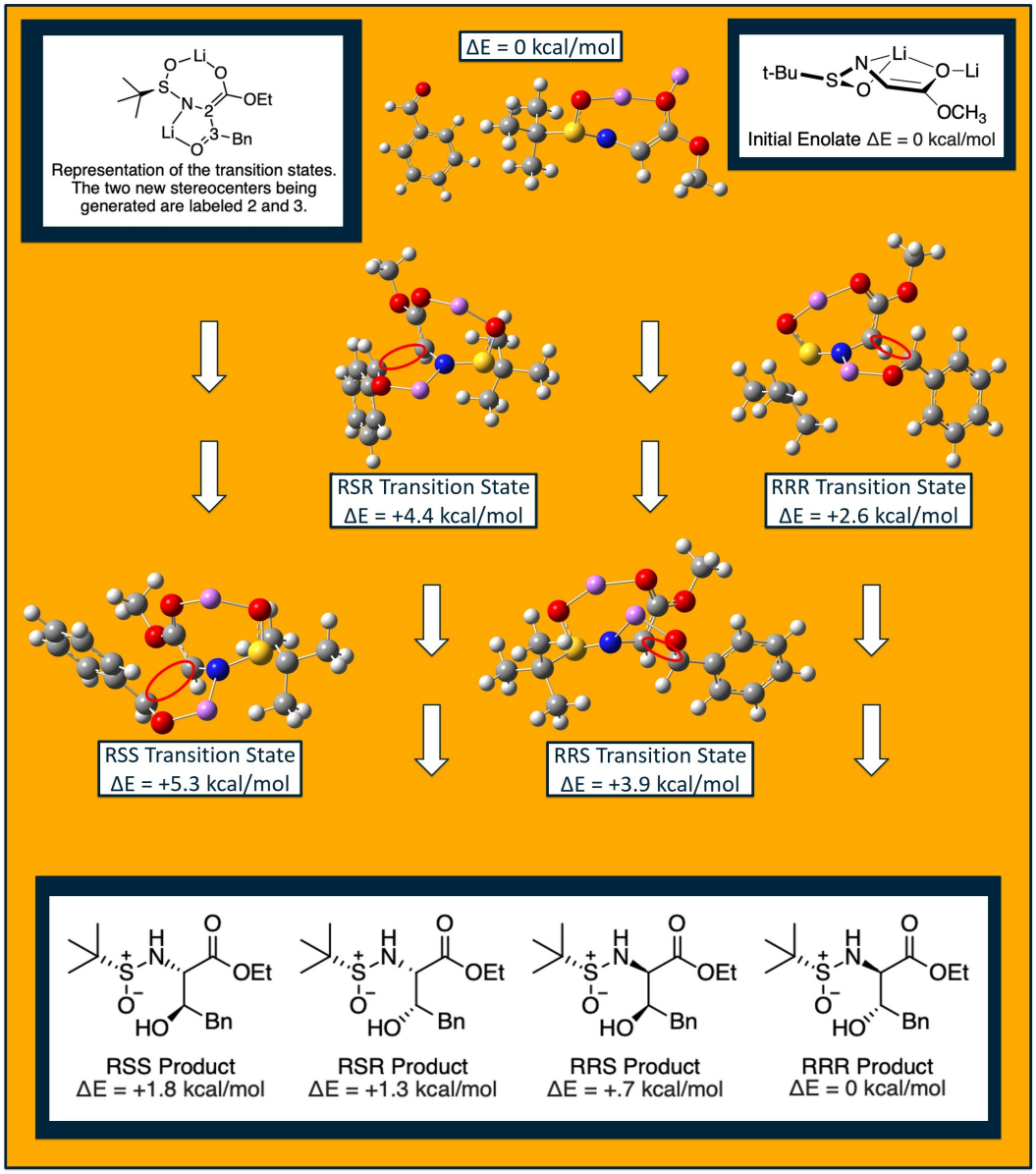
## I. Introduction

Chiral auxiliaries are used to bias the stereoselectivity of one or more subsequent reactions and are a valuable tool for enantioselective synthesis. These chiral auxiliaries store chiral information. Often, the added amide section of an added auxiliary does the selecting but it's also possible to have enolate-side auxiliary stereocontrol direct alkylations[1]. The diastereoselectivity of such a product is determined by the geometry and chelation of its enolate transition state leading to facial selectivity. Our goal in this computational investigation is to examine expanding this method to aldol reactions and ultimately inform our experimental work in lab.




## II. Methods

Exploring this potential further, performing an aldol reaction with a chiral enolate could also determine the stereochemistry of the new stereocenter generated from the added carbonyl along with the concomitant facial selectivity of the enolate. The energetics of this interaction can be estimated computationally. Using ground state DFT calculations using the B3LYP functional and 6-311+G(2d,p) basis set, the geometry and relative energies of the four relevant diastereomers and their transition states were calculated. All the transition states and diastereomers had the same connectivity but had slightly different geometries.




## III. Results

When considering reaction energetics, the product with a lowest energy transition state is kinetically favored while the product with the lowest energy is thermodynamically favored. The relative energies of the transition states are compared to the benchmark of the initial enolate and and benzaldehyde. The products are not isomers of the starting materials and therefore could only be compared to each other, benchmarked at the lowest energy RRR diastereomer. For all four diastereomers, a five membered transition state stabilizes the carbon-carbon bond forming event between the enolate and carbonyl of benzaldehyde. This stability is created by one of the lithium ions chelating the nitrogen adjacent to the enolate and the carbonyl of benzaldehyde.

## IV. Conclusions

From these results it can be determined that formation of the RRR diastereomer is both kinetically and thermodynamically favored. The RRR product has the lowest energy transition state and product. In the enolate alkylation, a 2.1 kcal/mol difference in relative energy led to a 6:1 dr of the the major product[1]. In the aldol reaction featured here the difference in relative energy of the RRR and RRS transition states is 1.3, significantly less. This could give the aldol a lower dr than the aforementioned alkylation. Moving forward, our computational investigation will consider other transition state geometries and substituting the lithium atoms for other metals

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(1) Dwulet, N.; Zolfaghari T.; Brown M.; Cannon, J.; Diastereoselctive Synthesis of Unatural Amino Acids by Alkylation ofα-tert-Butansulfinamide Auxiliary Bound Enolates. *J. Org. Chem.* **2018**, 83, 11510-11518