# Virtual Screening of New Potential Organocatalysts for Stereoselective Nitroaldol Reactions

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## INTRODUCTION

The reaction between an enolizable nitroalkane and a carbonyl compound, known as the Henry or nitroaldol reaction, is a very important synthetic tool for the creation of a carbon-carbon bond and up to two contiguous stereogenic centers.[1] Most catalysts have been discovery through serendipity or through empirical trial and error. Today computational are rapidly becoming a versatile tool for the rationalization and prediction of organocatalysts.[2] Here, we report our preliminary efforts toward generating models to predict enantioselection for the nitroaldol reaction.

## RESULTS AND DISCUSSION

The first step of this study involved the computational modeling of the Henry reaction between benzaldehyde and nitromethane applying 8 envisioned potential organocatalysts (Fig 1). DFT and PM6 calculations were carried out using GAUSSIAN 09.[3] All transition states were fully optimized using the M06-2X functional and PM6.

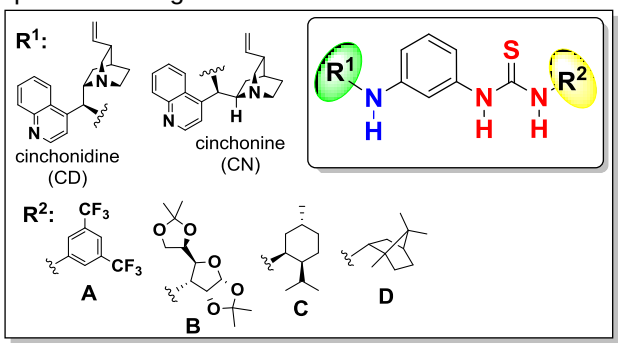


**Figure 1.** Bifunctional asymmetric catalysts for the stereoselective nitroaldol reaction.

The potential transition states of the enantioselectivity determining step of the Henry reaction involves the formation of carbon-carbon bond between the deprotonated nitromethane and benzaldehyde. The crucial aspect of this approach consists in the evaluation of the more stable conformations between catalyst and substrate in order to verify if these combinations allow the reactants to assume a key geometry favorable to the occurrence of the reaction. Catalysts candidates that do not meet these settings should be discarded.

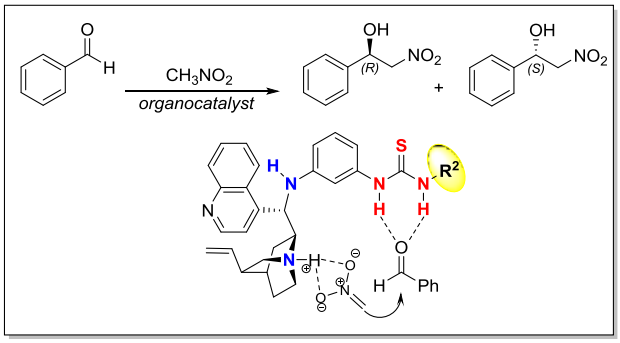


**Figure 2.** Transition state model for the reaction.

Table 1 presents the obtained data from the calculations in the gas phase of transition states for the formation of *R* and *S* enantiomeric products. Enantiomeric excesses in the range 88-99% were predicted for the prototype catalysts.

**Table 1.** Calculated substrate enantioselection for the reaction in Fig 2.

| Entry | Organocat. R1 | R2 | Calculated[a] ΔΔG*ee* (kcal/mol)[b] | *ee* (%)[c] | Calculated[d] ΔΔG*ee* (kcal/mol)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|
| **1** | CD | A | 1.49 | 88 | 1.69 | 91 |
| **2** | CD | B | 1.74 | 92 | 1.65 | 90 |
| **3** | CD | C | 2.09 | 96 | 1.51 | 89 |
| **4** | CD | D | 2.88 | 99 | 1.75 | 92 |
| **5** | CN | A | 2.71 | 98 | 1.49 | 88 |
| **6** | CN | B | 1.67 | 91 | 1.41 | 85 |
| **7** | CN | C | 1.94 | 94 | 1.75 | 92 |
| **8** | CN | D | 2.04 | 95 | 1.67 | 91 |

[a]M06-2X/6-311+G(2d,2p)//M06-2X/6-31G(d,p) level; [b]ΔΔG*ee* refers to the energy difference between the transition structures of the pathways leading to the *S* and *R* enantiomeric products; [c]values obtained from *ee* results by using ΔΔG=-RTln[(*S*)/(*R*)]; [d]M06-2X/6-31G(d,p)//PM6 level

## CONCLUSION

The molecular modeling results are optimistic, indicating that candidates have the potential for the enantioselective Henry reaction. Studies are underway to confirm experimentally these predictions.

## ACKNOWLEDGEMENTS

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## REFERENCES

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