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Enantioselectivity through Bisguanidinium Catalysis

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Introduction

Research into enantiomers sprang forth in the aftermath of the Thalidomide tragedy that resulted in thousands of children being born with severe birth defects. Pharmaceutical companies quickly realized that while a pair of enantiomers have the same chemical properties in achiral environments, they interact differently in the presence of other chiral molecules. So though seemingly identical, the difference in the spatial arrangement of the groups bonded to chiral carbon atoms may lead to drastically different outcomes, especially in the field of medication. One form holds the cure to illnesses, the R form in the case of thalidomide, and the other a catastrophe, the S form thalidomide.

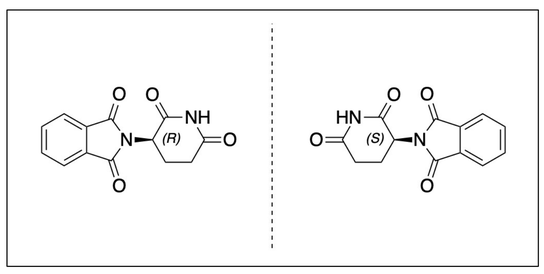


Figure 1 The enantiomer pair of thalidomide, which are the mirror image of each other.

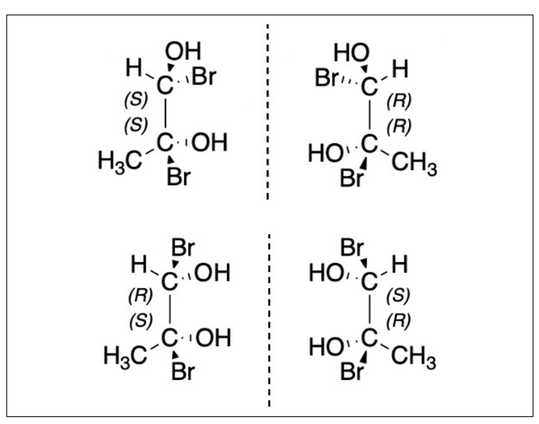


Figure 2 Diastereomers are non-mirror image non-identical stereoisomers. Any one of the top enantiomer is the diastereomers of any one of the bottom enantiomer, and vice versa.

Such a difference in how the body reacts to the different enantiomeric forms has been observed in other drugs, driving the need for the isolation of enantiomerically pure synthetic products. This has proved to be challenging due to the identical physical properties of a pair of enantiomers. Currently, the most established way of chiral resolution is by converting enantiomers to diastereomers. Developed on the basis that diastereomers have significantly different physical properties, the separated diastereomers by physical means would then be hydrolyzed to procure back the now enantiomerically pure R and S enantiomers. This post-synthesis procedure can be complex and tedious, and so obtaining the pure enantiomer forms have taken a new direction in recent years - asymmetric catalysis.

Asymmetric catalysis brings the selection of the desired enantiomer form into the synthesizing step. Using enantioselective catalysts in the reaction mixture, the resultant product is no longer a racemic mixture but nearly enantiomerically pure under optimized conditions.

Research Content

Bisguanidinium(BG) is a specially design enantioselective catalyst, that carries two positive charges. It facilitates the enantioselection first through ion pairing with negatively charged reaction catalysts, which fit into the two big 'pockets' of BG. Figure 4 shows one possible way of visualizing the 'pockets'. Due to the bulky side chains of BG, the reactant molecules would approach from the direction not sterically hindered by them, thus resulting in the enantioselective synthesis.

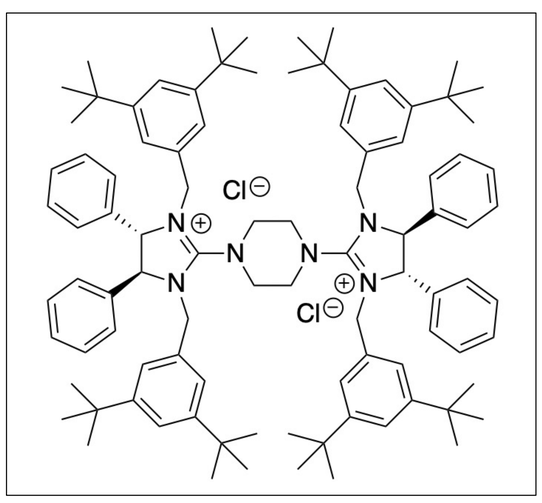


Figure 3 Structure of bisguanidinium.

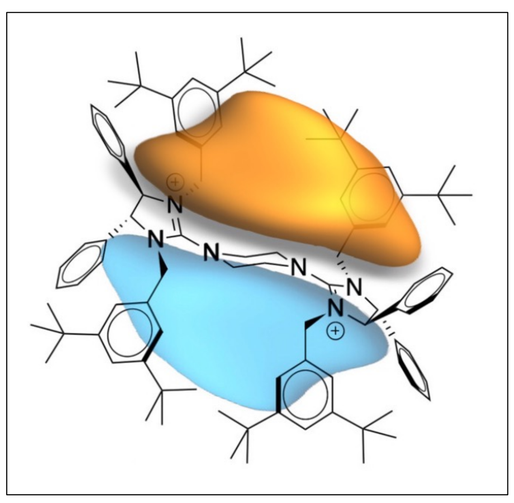


Figure 4 Visualization of the BG 'pockets'.

Two reactions were studied. The first was benzoin condensation catalyzed by thiamine, figure 5. The second was 1,4 – Michael addition with condensation catalyzed by pyridoxal bisphosphate.

Benzoin Condensation

After several attempts to synthesize benzoin, it was realized that this reaction is not compatible with BG as the enantioselective catalyst. Post reaction analysis shows that the mechanism that this reaction proceeds by inactivates BG as it destroys by cleaving several crucial bonds in the BG molecule.

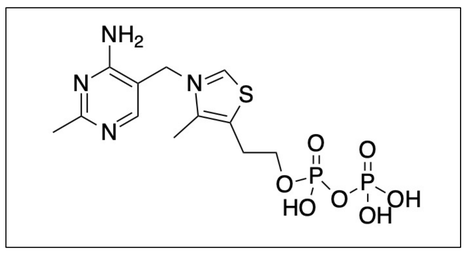


Figure 5 Thiamine

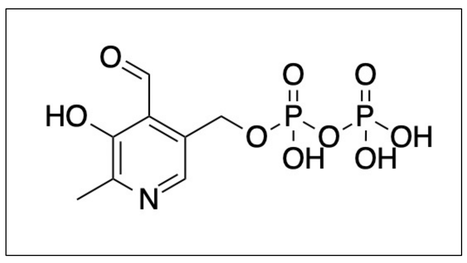
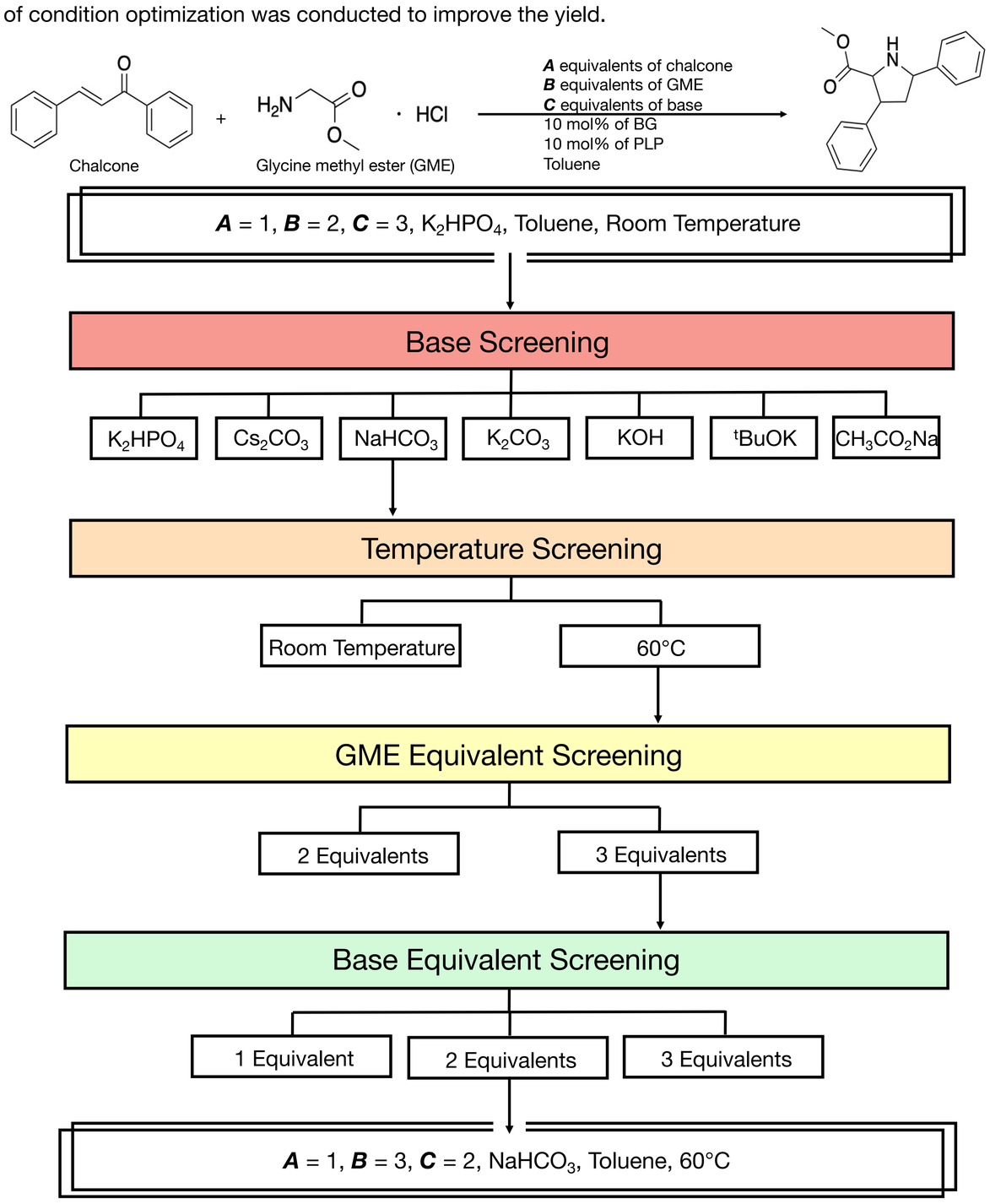


Figure 6 Pyridoxal bisphosphate

1,4 – Michael Addition with Condensation

Previous studies conducted have proven that this reaction is compatible with BG and enantioselectivity can be induced. However, the yield of this reaction was very low and thus a series of condition optimization was conducted to improve the yield.



Condition Optimized	Time (h)	Yield (%)
None (Initial conditions)	66	< 10
Base	66	< 20
Temperature	70	29.4
GME Equivalents	52	32.3
Base Equivalent (Final conditions)	80	48.7

Table 1 Results of yield condition optimization

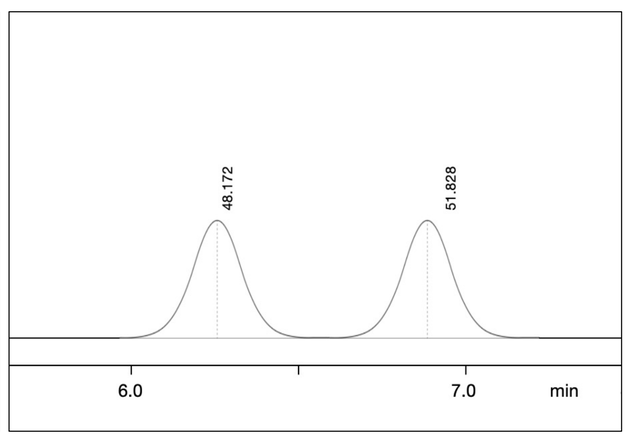


Figure 7 HPLC analysis of the major diastereomer pair product, with retention times of 6.1 and 6.8 min, under the final conditions.

Discussion

Other than the conditions tested above, other factors can be tested. For example, different solvent systems, reactant concentrations in solvent, more narrowed range of equivalents of GME and base can be tested to further increase the yield. However, while it is evident that the yield has significantly increased, there is a drawback in terms of the enantioselectivity induced. Figure 7 shows that there is no significant selection of the enantiomers. This clearly showcases the conflict between optimizing the yield and optimizing the enantioselectivity as they often require opposing conditions, for example, higher temperature for better yield but lower temperature for better enantioselection. A fine balance between yield and enantioselection needs to be stroked when selecting the conditions in optimization.

Conclusion

One advantage of BG lies in its versatility, where it is not restricted to just one reaction scheme. However, it can be concluded that BG may not be the enantioselective catalyst for all types of reactions due to incompatibility. For those that can pair well together, there may also be cases where it is unable to obtain the ideal outcome of both high yield and excellent enantioselection.