Mechanistic Intricacies of Photochemical Deracemization

Reported by Henry Cavanaugh October 22nd, 2024

Introduction

Due to the chirality of proteins and other biomolecules, the enantiomeric identity of small-molecule drugs can have profound implications for their biological activity.[1] As a result, development of methods for efficient enantioselective synthesis of bioactive molecules has remained a longstanding pursuit within organic chemistry. In particular, resolution processes, in which undesirable enantiomers are selectively removed, have proven exceptionally useful. With that being said, deracemization reactions offer generally higher yields due to formation of the desired enantiomer during the course of the reaction. However, because deracemization processes are inherently endothermic, enantioselectivity cannot be achieved through traditional approaches to asymmetric catalysis.[2] To this end, photochemistry has been shown to be an effective solution. Especially in recent years, the field has seen a resurgence of interest associated with many intellectually and practically significant advances.[3-6]

Energetic Considerations

The birth of the field of small-molecule asymmetric catalysis is often attributed to the development of the Nobel-prize winning Monsanto L-Dopa process. This process demonstrated for the first time that the interaction of a substrate with a chiral small-molecule catalyst could produce meaningful differences between energy barriers leading to each enantiomer. Similar logic is applied in kinetic resolutions, relying on the irreversible, exothermic nature of the targeted transformation in order to achieve selectivity.[2] In contrast, for endothermic processes such as deracemization, the reverse direction is always accessible under reaction conditions and is favored in exact proportion to the forward reaction, as the system exists in a state of equilibrium.[3] A comparison of energy diagrams can be observed in *Figure 1*. The challenge posed by microscopic reversibility necessitates separation of the forward and reverse pathways for endothermic enantioselective reactions.

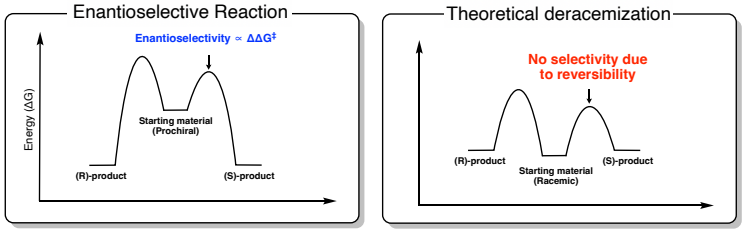

Figure 1. Free energy diagrams depicting the origin of enantioselectivity, or lack thereof in generic asymmetric catalysis and hypothetical deracemization.

Stereochemical Enrichment via Photochemical Resolution

The work of Bach and coworkers towards photochemical deracemization of cyclic hydantoin molecules exemplifies the most common approach to the field, which relies on chiral photosensitizers to selectively racemize/planarize one enantiomer over the other, leading to multiplicative enhancement of the desired enantiomer.[4,5] This concept is depicted by *Figure 2*. After selective planarization, the generated intermediates follow a thermal pathway back to the starting material, which will typically lead to

racemization unless another chiral catalyst is introduced. However, whether or not this alternative reverse reaction is either selective for the desired enantiomer or leads to racemization, this process will enhance the enantiopurity of the solution in a cyclic manner.

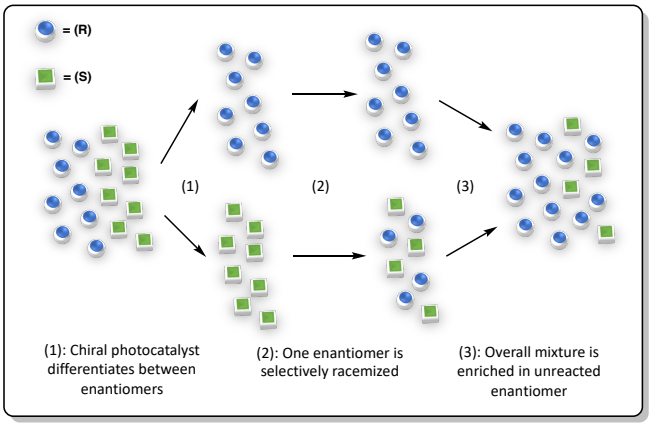

Figure 2. Simplified overview of the concept of multiplicative enhancement of chirality.

While use of a chiral photocatalyst is the most common starting point for develop of these systems, it is not the sole approach. Indeed, Robert R. Knowles and coworkers demonstrate photochemical deracemization of cyclic ureas through use of an achiral iridium photocatalyst alongside a chiral base and proton source.[3] In this system, both enantiomers undergo photoexcitation to a radical cation intermediate, and a chiral base is able to differentiate between these high-energy intermediates. While the desired enantiomer is re-formed from this high-energy intermediate by reverse reaction with the photocatalyst, the undesired enantiomer is planarized and subjected to a chiral acid, leading again to multiplicative enrichment of the desired enantiomer.

Stereochemical Enrichment via Photochemical Isomerization

Finally, Luo and coworkers demonstrated a remarkably distinct approach, using photochemistry to isomerize a thermally generated planar intermediate.[6] By combining chiral amines with aldehydes, these researchers accessed enamine intermediates which are rapidly isomerized via light to the thermodynamically disfavored (Z)-enamine, as depicted in *Figure 3*. This isomerization decouples the forward and reverse reactions and creates a kinetic bias that will form one enantiomer faster than the other, leading to enrichment.

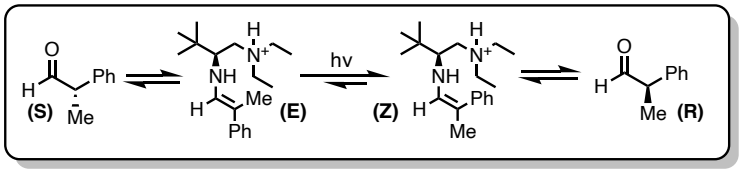

Figure 3. Biased kinetic profile exploited by Zuo and coworkers.

Outlook

The field of photochemical deracemization has seen accelerated development in recent years and appears poised to move towards industrial application. However, scope remains limited and reliance on expensive Nobel-metal photocatalysts precludes large-scale use. Intentional focus on improving the industrial viability of these reactions as early-stage purification methods could improve upon existing approaches (*e.g.* kinetic resolution) and could enable greater societal impact.

References

(1) *Curr. Top Med. Chem.* **2011**; 11(7): 760–770
(2) *Science* **2019** 366, 304-305.
(3) *Science*, **2019**, 366, 364-369
(4) *J. Am. Chem. Soc.,* **2023**, 145 (4), 2354-2363
(5) *J. Am. Chem. Soc.* **2021**, 143, 21241−21245
(6) *Science*, **2022**, 375, 869-874