STEREOEDITING VIA ASYMMETRIC HYDROGEN ATOM TRANSFER

Reported by Haonan Chen September 30, 2025

Introduction

Currently, complex molecules with sp^3 carbon stereocenters are typically constructed by desymmetrization of non-stereogenic centers or the assembly of chiral building blocks (Figure 1a).[1] These case-by-case strategies rely on directing groups and unique stereoselective conversions. In contrast, the direct editing of stereocenters enables the accurate tuning of configuration with a more general, late-stage method. By stereoediting, all stereoisomers can be interconverted. Such precise manipulation greatly extends the present chiral pools and simplifies the synthesis (Figure 1b).[2]

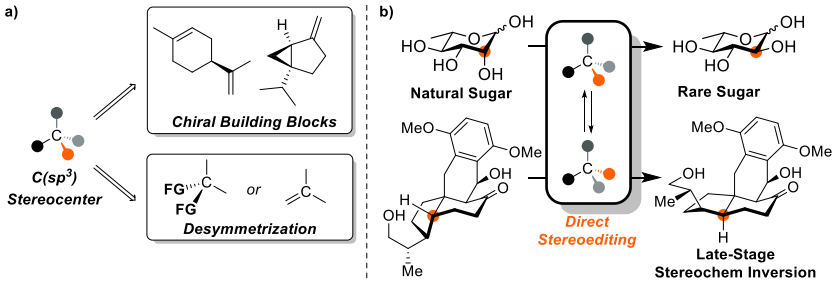

Figure 1. Strategies to construct sp^3 carbon stereocenters stereoselectively.

C-H Epimerization via Double Hydrogen Atom Transfer

Rigid tertiary carbon stereoediting remains challenging owing to the strength of the C-H bond. A solution was inspired by a stereoediting enzyme, *S*-adenosyl-L-methionine epimerase.[3] The enzymatic epimerization involves two consecutive hydrogen atom transfers (HAT): hydrogen atom abstraction (HAA) followed by hydrogen atom donation (HAD). This double HAT process triggers the structural change from neomycin C to its epimer, neomycin B (Figure 2).

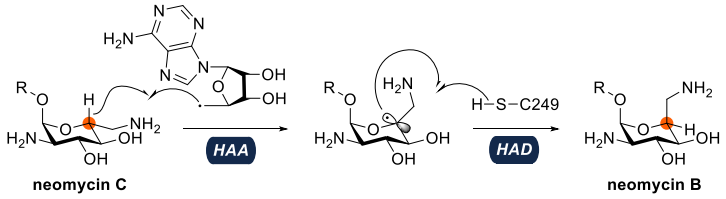

Figure 2. Biosynthetic example of C-H epimerization.

To mimic the double HAT in biosynthesis, HAA via proton-coupled electron transfer (PCET) was coupled with HAD from a thiol.[4] A photocatalyst (PC) and a base (B) mutually cleave the C-H bond and generate a tertiary radical. HAD from the thiol (RSH) regenerates the C-H bond and yields the new, biased epimer (Figure 3, left). *In situ* radical catalyst generation can also be applied to effect epimer interconversion (Figure 3, right).[5] C-H epimerization successfully converted diols, multi-substituted rings,

and fused ring systems to their thermodynamically-favored epimers.[2,6] Nonetheless, this double HAT process cannot resolve enantiomers because they are isoenergetic.

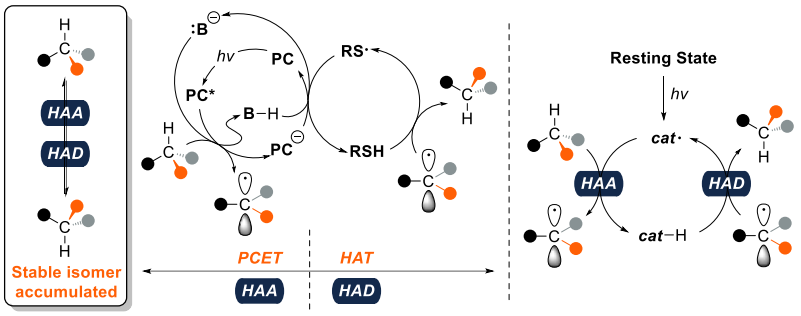

Figure 3. Accumulation of thermodynamically-favored epimers via double HAT.

Deracemization via Irreversible, Enantioselective HAT

Mechanistic studies showed that irreversible HAT can be achieved in C-H epimerization by suppressing thiol deprotonation.[7] This discovery guided the design of new chiral HAT catalysts such as cinchonidine derivatives[8] and tetrapeptide thiols[9] (Figure 4). Meanwhile, benzophenones, whose back-HAT is forbidden, were modified to achieve enantioselective HAT in their triplet state.[10] By retaining the enantioselectivity and irreversibility, these catalysts can successfully convert the racemic mixtures to enantioenriched products.[8,9,10]

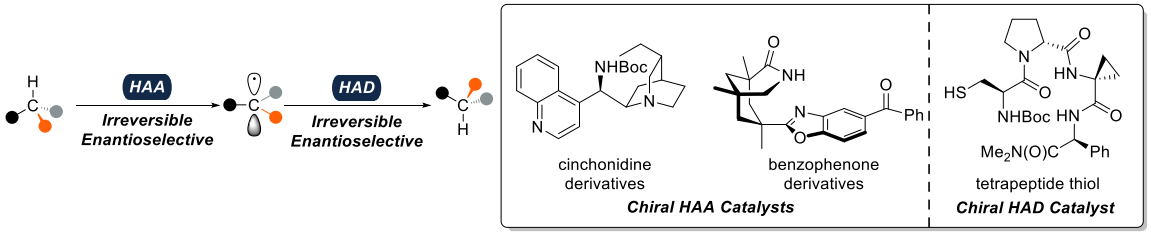

Figure 4. Catalyst design for asymmetric HAT.

References

(1) Selka, A.; Abidli, A.; Schiavo, L.; Jeanmart, L.; Hanquet, G.; Lubell, W. D. *Eur. J. Org. Chem.* **2025**, *28*, e202400983.
(2) Carder, H. M.; Wang, Y.; Wendlandt, A. E. *J. Am. Chem. Soc.* **2022**, *144*, 11870.
(3) Hoskin, J. F.; Sorensen, E. J. *J. Am. Chem. Soc.* **2022**, *144*, 14042.
(4) Kudo, F.; Hoshi, S.; Kawashima, T.; Kamachi, T.; Eguchi, T. *J. Am. Chem. Soc.* **2014**, *136*, 13909.
(5) Shen, Z.; Walker, M. M.; Chen, S.; Parada, G. A.; Chu, D. M.; Dongbang, S.; Mayer, J. M.; Houk, K. N.; Ellman, J. A. *J. Am. Chem. Soc.* **2021**, *143*, 126.
(6) Zhang, Y.-A.; Palani, V.; Seim, A. E.; Wang, Y.; Wang, K. J.; Wendlandt, A. E. *Science* **2022**, *378*, 383.
(7) Wang, Y.; Carder, H. M.; Wendlandt, A. E. *Nature* **2020**, *578*, 403.
(8) Lahdenperä, A. S. K.; Dhankhar, J.; Davies, D. J.; Lam, N. Y. S.; Bacoş, P. D.; de la Vega-Hernández, K.; Phipps, R. J. *Science* **2024**, *386*, 42.
(9) Yan, X.; Pang, Y.; Zhou, Y.; Chang, R.; Ye, J. *J. Am. Chem. Soc.* **2025**, *147*, 1186.
(10) Iglhaut, M.; Bach, T. *Acc. Chem. Res.* **2025**, *58*, 777.