Towards Chiral Recognition by Design. Uncovering the Self-Enantioresolving Properties of Chiral Amine Derivatives.

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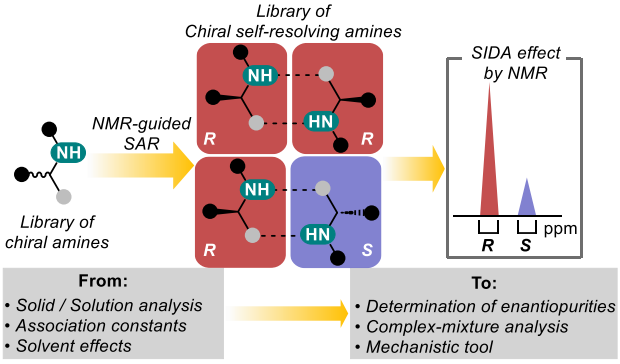
The study of chiral recognition phenomena is critical for understanding biological processes and designing bioactive compounds.[1] In addition, phenomena related to the self-recognition of enantiomers are highly relevant in emergence-of-homochirality research and supramolecular chemistry.[2-4] However, the design of molecules exhibiting chiral self-recognition remains challenging and its observation is mainly based on serendipity.[5] Here we report a comprehensive study on the self-enantiorecognition properties of chiral amine-derived building blocks frequently encountered in organic synthesis. Through a structure-activity relationship study, multiple families of chiral amine derivatives, featuring self-complementary hydrogen-bond donor and acceptor groups, have been found to exhibit self-induced diastereomeric anisochronism (SIDA) by NMR, a rather unexplored form of self-recognition of enantiomers. Our study suggests that the self-enantiorecognition properties of many common building blocks in asymmetric synthesis might have remained inadvertently unnoticed. We have also rationalized the origins of their SIDA effect and demonstrated its potential as an in situ probe for the determination of enantiomeric purity, the analysis of supramolecular interactions and the study of reaction mechanisms. We anticipate that the principles outlined here will contribute to fostering the use of the SIDA effect in fundamental stereochemical studies, asymmetric synthesis, catalysis, and supramolecular chemistry.



1. Peluso, P.; Chankvetadze, B. *Chem. Rev.* **2022**, *122*, 13235
2. Buhse, T.; Cruz, J.-M.; Noble-Terán, M. E.; Hochberg, D.; Ribó, J. M.; Micheau, *Chem. Rev.* **2021**, *121*, 2147
3. Blackmond, D. G. *Chem. Rev.* **2020**, *120*, 4831-4847
4. Bryliakov, K. P. *ACS Catal.* **2019**, *9*, 5418-5438
5. Szakács, Z.; Sánta, Z.; Lomoschitz, A.; Szántay, *Trends Anal. Chem.* **2018**, *109*, 180