Advancing Molecular Editing Through Nitrogen Atom Edits: From Fundamental Reactivity to Late-Stage Functionalization

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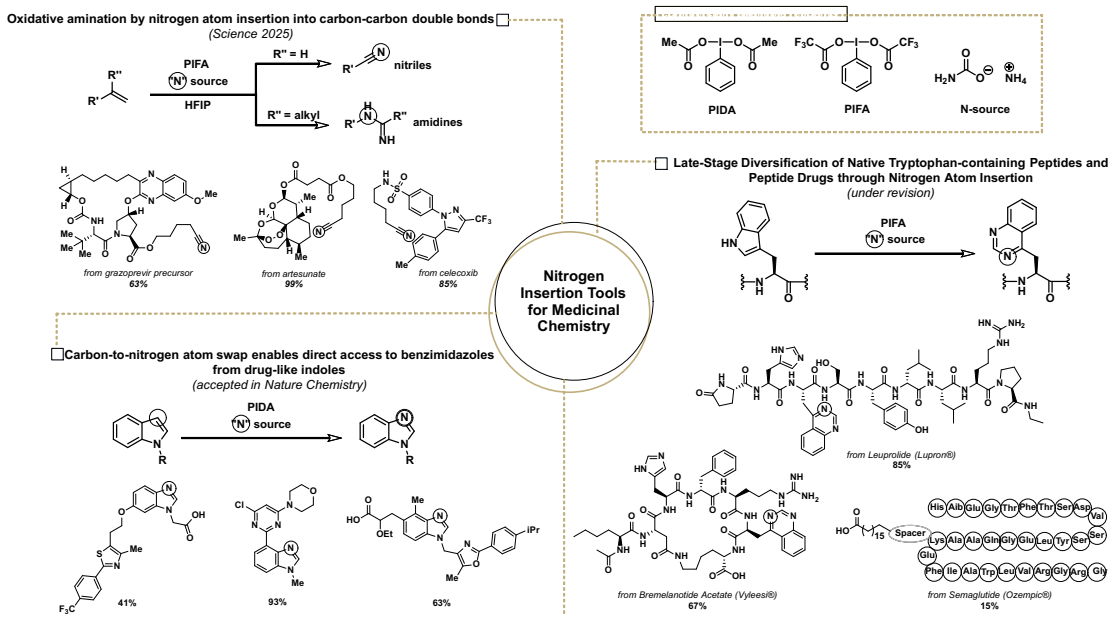
Skeletal editing has emerged as a promising strategy to rapidly diversify chemical matter without time-consuming *de novo* synthesis. Direct modification of the molecular core offers a new tool in hit explosion, lead discovery, and the study of structure-activity relationships (SARs) using existing compound libraries. Herein, we present our developed methods for the late-stage diversification of small molecule and peptide drugs: A) Building on our groups work,[1] we recognized the potential for applying skeletal editing on tryptophan-containing peptide drugs and demonstrated the first core remodelling of peptides in collaboration with the Grob lab (ETHZ). The method was successfully applied to cyclic and linear peptide drugs in up to 85% yield.[2] B) Pushing beyond activated systems, like indoles, we developed a method to insert nitrogen into unactivated C-C double bonds, accessing nitriles from linear alkenes and amidines from branched alkenes with exceptional functional group tolerance.[3] C) While nitrogen insertions alter the molecular topology, diminishing the utilization in SAR studies, the precise exchange of one atom with another offers a complementary tool for lead optimization. We developed a C-to-N atom swap protocol which uses native indoles to furnish benzimidazoles. With the successful application to 15 lead-like structures (gratifyingly received from Hoffmann-La Roche) with up to 93% isolated yield, we could confidently claim the broad applicability of our method to complex, industrially relevant scaffolds.[4]



[1] J.C. Reisenbauer,† O. Green,† A. Franchino, P. Finkelstein, B. Morandi, *Science* **2022**, *377*, 1104–1109.
[2] **A-S.K. Paschke,**† E.J. Meeus,† M. Masota, F. Hoffmann, N.M. Grob, B. Morandi, *Under revision*.
[3] Y. Brägger,† **A.-S.K. Paschke,†** N. Nasiri, B.B. Botlik, F. Felician, B. Morandi, *Science* **2025**, *387* (6738), 1108–1114.
[4] **A.-S.K. Paschke,** Y. Brägger, B.B. Botlik, E. Staudinger, O. Green, B. Morandi, *Nat. Chem.* **2025**, *17*, 1750–1756.