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# Swiss Science Concentrates

## A CHIMIA Column

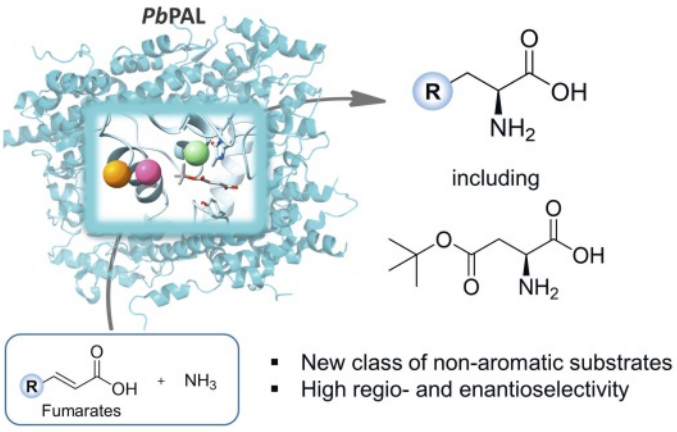
Short Abstracts of Interesting Recent Publications of Swiss Origin

### Engineered Phenylalanine Ammonia-Lyases for the Enantioselective Synthesis of Aspartic Acid Derivatives

Ivan Buslov, Sarah Desmons, Yoan Duhoo, and Xile Hu*
*Angew. Chem. Int. Ed.* **2024**, *63*.
https://doi.org/10.1002/anie.202406008
Ecole Polytechnique Fédéral de Lausanne

This article reports on the engineering of phenylalanine ammonia-lyases (PALs) for the enantioselective synthesis of aspartic acid derivatives *via* biocatalytic hydroamination of alkenes. PALs typically suffer from a limited substrate scope and demonstrate poor enantioselectivity with electron-deficient substrates. The study employs structure-based engineering of PALs from *Planctomyces brasiliensis* (PbPAL), identifying the active site residue L205 as critical for enhancing enantioselectivity. The engineered PALs exhibit high α-regioselectivity, enantioselectivity, and a broad substrate range, enabling preparative-scale hydroaminations of previously inaccessible substrates like amide and ester containing fumaric acid derivatives. These advancements were demonstrated by producing *tert*-butyl protected L-aspartic acid, a key intermediate in peptide synthesis. This work highlights the potential of biocatalysis for synthesizing amino acids under mild conditions with tunable selectivity, extending the industrial applications of C–N lyases and marking a significant step forward in the field.

**Authors' comments:**
"We were excited to convert phenylalanine ammonia lyase, traditionally limited to aromatic amino acids, into biocatalysts producing valuable aspartic acid derivatives. Controlling hydroamination enantioselectivity opens new opportunities for this enzyme class."

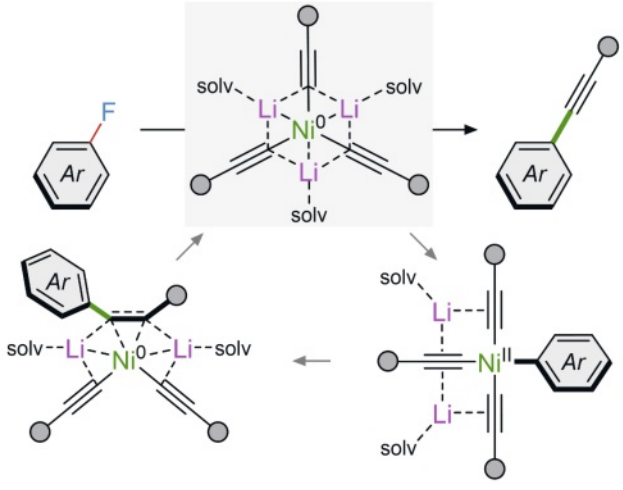



### Stoichiometric and Catalytic Lithium Nickelate-Mediated C–F Bond Alkynylation of Fluoroarenes

Andryj M. Borys, Luca Vedani, and Eva Hevia*
*J. Am. Chem. Soc.* **2024**, *146*, 10199.
https://doi.org/10.1021/jacs.4c02606
Department für Chemie, Biochemie und Pharmacie, Universität Bern, Switzerland.

Low-valent nickelates are crucial intermediates in enabling difficult cross-coupling reactions. This study presents trilithium nickelate $Li_3(TMEDA)_3Ni(C{\equiv}C{-}Ph)_3$ which enables stoichiometric C–F activation of aryl fluorides, generating unique Li/Ni(0) or Li/Ni(II) species. These stoichiometric processes can be adapted to catalytic conditions and enable efficient alkynylation of aryl fluorides and polyfluoroarenes with lithium acetylides and $Ni(COD)_2$ precatalysts without the need for external ligands or cocatalysts. This work presents the first Ni-catalyzed alkynylation of aryl fluorides, bypassing the need for Pd or Cu cocatalysts. Their results extend the range of catalytic reactions possible with low-valent nickelates and provide important mechanistic insights into C–F activation.

**Authors' comments:**
"After recognising early on that alkali-metal nickelates react with PTFE stirrer bars, we succeeded in taming these heterobimetallic complexes towards selective C–F bond activation under stoichiometric and catalytic conditions."




Prepared by Patrick A. Cieslik, Cesare Berton, Simon Klingler, Jonas Genz, Stanislav Prytuliak, Fan Liu, Eda Nisli, Deborah Bäcker, Perle Hermant, Samy Kichou, Ben Boback, Henrik Braband, and Jason P. Holland*
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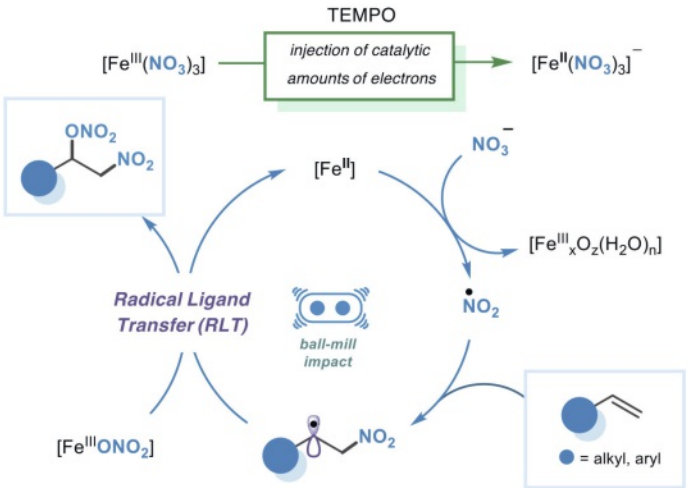
## Mechanochemistry Drives Alkene Difunctionalization *via* Radical Ligand Transfer and Electron Catalysis

Subrata Patra, Bhargav N. Nandasana, Vasiliki Valsamidou, and Dmitry Katayev*
*Adv. Sci*., **2024**, *11*, 2402970
https://doi.org/10.1002/advs.202402970
Department für Chemie, Biochemie und Pharmacie, Universität Bern, Switzerland.

In this study, a novel and versatile method for olefin difunctionalization using mechanochemistry has been developed, featuring cooperative radical ligand transfer (RLT) and electron catalysis. The process uses mechanochemical force and catalytic amounts of TEMPO, allowing ferric nitrate to liberate nitryl radicals, transfer a nitrooxy-functional group *via* RLT, and mediate an electron catalysis cycle at room temperature. This approach efficiently produces chemo- and regioselective 1,2-nitronitrooxylation across a wide variety of activated and unactivated alkenes, under solvent-free or solvent-less conditions, demonstrating excellent tolerance to different functional groups. Mechanistic studies reveal the crucial role of mechanochemistry and the radical nature of this novel nitrative difunctionalization process.

**Authors' comments:**
"Enabling radical ligand transfer (RLT) and electron catalysis through mechanochemistry facilitates single electron transfer (SET) transformations with minimal to no solvents. While the primary focus has been on incorporating *N*-centered functional groups, we anticipate that this versatile platform can be adapted to simultaneously introduce two different functionalities across an olefin's π-bond, thereby unlocking new chemical space."




## Development of Supermolecular Anticoagulants with On-Demand Reversibility

Millicent Dockerill, Daniel J. Ford, Simona Angerani, Imala Alwis, Luke J. Dowman, Jorge Ripoll-Rozada, Rhyll E. Smythe, Joanna S. T. Liu, Pedro José Barbosa Pereira, Shaun P. Jackson, Richard J. Payne, and Nicolas Winssinger*
*Nat. Biotechnol*. **2024**,
https://doi.org/10.1038/s41587-024-02209-z
University of Geneva

The administration of drugs is governed by their therapeutic index, with the cessation of their action dependent on clearance and metabolism. However, a significant challenge arises with certain drugs, such as anticoagulants and immunotherapeutics, which may require rapid cessation in case of adverse effects. This study addresses this issue by proposing a novel strategy for on-demand reversibility through the design of a supramolecular drug. This drug consists of two fragments held together by the transient hybridization of peptide nucleic acid (PNA), forming a noncovalent assembly. The drug's action can be reversed by a PNA antidote that disrupts the hybridization. Demonstrated with thrombin-inhibiting anticoagulants, the approach yielded potent, reversible bivalent thrombin inhibitors ($K_i$ = 74 pM). In mouse models, the inhibitor successfully prevented thrombus formation and was reversible with the PNA antidote. This design is applicable to therapeutic targets with two identifiable binding sites.

**Authors' comments:**
"We are excited to show that basic supramolecular circuitry can be used to prepare inhibitors with a built-in mechanism for fast reversal of action. This was applied to thrombin inhibition, a clear case where a fast reversal of action can be warranted. In the broader context, it is exciting to show that simple nucleic acid networks can operate efficiently in a mammalian model, this opens the door to smarter therapeutic responses. This work was made possible by a great collaboration with the Payne, Jackson, and Barbosa Pereira labs."