ADVANCING SUSTAINABLE SYNTHESIS: BRIDGING DIGITALIZATION AND EXPERIMENTAL INNOVATION

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Synthesis as a Driver of Innovation - Balancing Efficiency, Innovation and Responsibility

Organic synthesis is a central driver of innovation in modern society, with small organic molecules securing our health, food supply and improving everyday life as colorants, fragrances, flavourings or innovative materials. As the world faces growing challenges from climate change to limited resources, the need for new, efficient and more sustainable molecular solutions is becoming increasingly clear. Meeting these challenges will require not only discovering new molecules more quickly, but also rethinking how we make them. Catalysis is central to this transition. It enables more selective, energy-efficient and less wasteful chemical transformations, and beyond that has enabled a range of transformations previously considered impossible. Today, the continued evolution of catalysis stands to benefit greatly from the integration of digital tools, particularly computational chemistry and machine learning. Owing to tremendous advances in theory, algorithms and computing power, chemical reactivity can nowadays be simulated and predicted with a level of speed and accuracy that is competitive with (or even faster than) doing experiments. These capabilities open up new opportunities to (i) predicting and designing chemical reactivity with minimal experimental input, thereby saving time, reducing costs and minimizing waste; and (ii) revealing new mechanistic insights at the molecular level, enabling the discovery of entirely new transformations and the rational design of next-generation catalytic systems.

My recent research contributions to the session's theme: *sustainable synthesis*

Over the past 15 years, our group has conducted research at the interface of synthetic organic, mechanistic and computational chemistry, with a strong emphasis on homogeneous catalysis (Fig. 1). By uniting digital and experimental strategies, we aim to move beyond intuition- or trial-and-error-driven discovery toward a design-and-simulate paradigm. This integrated approach not only supports more informed decision-making but also uncovers new reactivity principles and enables the prediction of catalysts and reagents before they are experimentally realized.

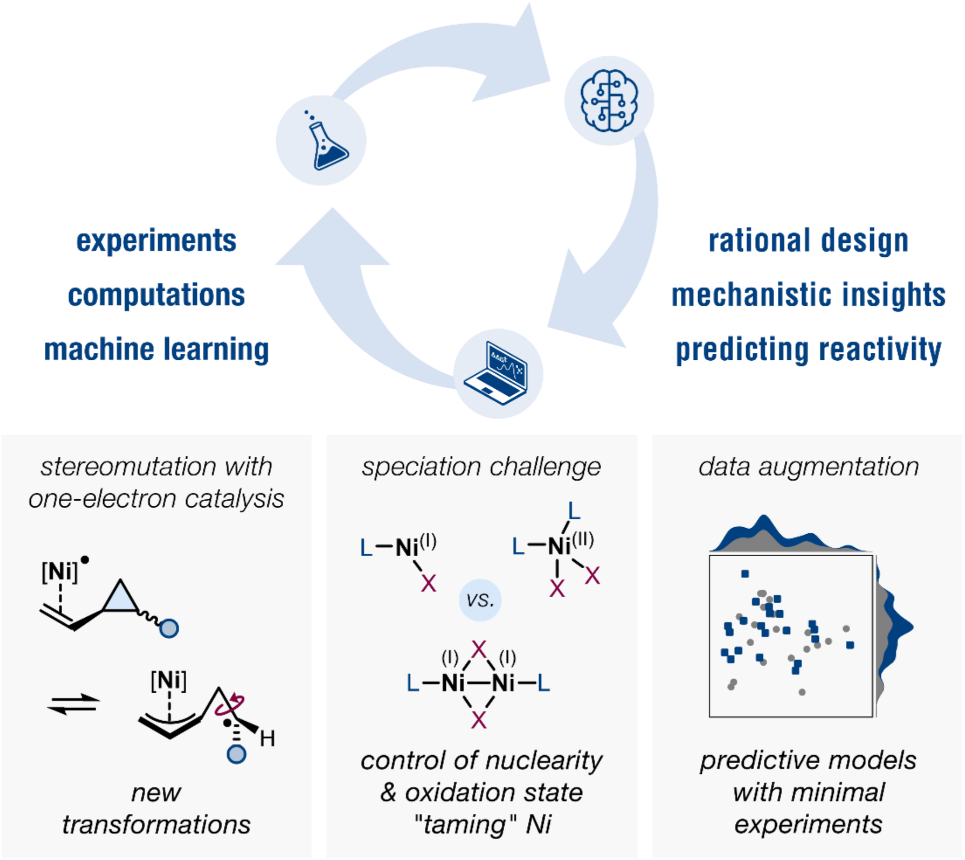

Fig. 1. Integrating experimental, computational and machine learning approaches for reactivity developments.

Example 1. *Computational and ML insights driving experimental advances: Ni-catalyzed dynamic stereomutation.*

To meet the demand for sustainable, low-energy chemical processes, the identification of fundamentally new reactivity concepts will be imperative. In this context, the ability to directly mutate molecules to access alternative isomers, while avoiding lengthy and resource-intensive multistep syntheses, is especially appealing. Leveraging the unique potential of odd oxidation states in non-precious metals, we recently showed that Ni(I) metalloradicals defy conventional paradigms [1,2]. Instead of ring-opening in vinylcyclopropanes, the non-precious Ni(I) catalyst triggers rapid, reversible *cis/trans* isomerization with stereoinversion at room temperature in under 5 minutes [2]. Quantum mechanical calculations and experimental studies revealed metalloradical catalysis as the origin of this reactivity, and the molecular insight inspired the realization of an iterative thermodynamic stereomutation towards single isomers. In extension to divinylcyclopropanes, *i.e.* strategic motifs in total synthesis, we showed that while classical *trans→cis* isomerization requires ~200 °C and causes racemization, Ni(I) catalysis achieves the *contra*-thermodynamic transformation under mild conditions with, for the first time, complete stereochemical integrity, offering not only a more sustainable solution but also a powerful new tool for synthesis [2].

Example 2. *Speciation and reactivity challenges in sustainable metal catalysis: abundant metals offer greater oxidation state diversity, but are harder to control? A machine learning solution.*

The *in situ* fate of a catalyst or intermediate, *i.e.* its speciation, critically shapes catalytic efficiency, reactivity and selectivity. Precious metals typically adopt stable oxidation states and nuclearities, but less precious, more sustainable metals readily shift between states, dimerize or deactivate, often limiting scope and selectivity [3]. These speciation factors remain poorly understood, with trial-and-error dominating catalyst development. To overcome this, we developed an unsupervised machine learning workflow that requires only minimal experimental input (as few as two experimental data points) and builds an *in silico* database through calculation, followed by algorithmic similarity searching [4]. This approach successfully predicted metal dimers of oxidation state (I) [4,5], including ligands from unexplored chemical space, and Ni(I)–phenyl monomers [6], which are key intermediates in CO_2 functionalization. The model identified ligands that stabilize Ni(I)–aryl complexes and render them reactive with CO_2 at room temperature.

Example 3. *Smarter, leaner, greener: building predictive models with minimal experiments.*

Data scarcity remains a major obstacle to harnessing the predictive power of AI for chemical reactivity [7,8], where models must capture subtle steric, electronic and structural effects. In the context of sustainable synthesis, this limitation translates into excess experimentation, higher ressource use and more waste. To address this, we explored data augmentation, a strategy well established in fields like image and speech recognition, as a route to build predictive reactivity models with less data. By introducing Gaussian noise to existing datapoints, full datasets can be expanded in seconds, dramatically improving model performance especially in low-data regimes. This approach enables meaningful predictions with only a fraction of the data, reducing the need for additional experiments by 20–50% [9]. In doing so, it not only conserves time, energy and resources but also establishes data augmentation as a powerful strategy to accelerate machine-learning-driven advances in molecular reactivity in a more sustainable fashion.

Outlook on Sustainable Synthesis

Looking ahead, the steadily expanding repertoire of synthetic methods, together with deeper insight into chemical processes and the accelerating role of digital tools, points to a future where sustainability can be integrated more naturally into practice. In addition, growing awareness and commitment within the community make the transition towards sustainable molecule-making not only feasible but increasingly likely.

Ambitious goals, such as achieving circularity and advancing more reagent and waste recycling, will benefit from wider, coordinated initiatives. Yet the breadth of ‘sustainable synthesis’ should be seen as an opportunity: it allows priorities to evolve dynamically alongside global developments. As the energy system shifts toward renewable sources, new cost structures will open up possibilities for recycling and resource efficiency. This evolving context holds the promise of reshaping synthesis in ways that are both innovative and more sustainable.

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