

Covalent Amine–Graphene Oxide Interface for Dispersed Mixed-Valence Palladium Nanostructures and Sustainable Cross-Coupling

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GO is a two-dimensional carbon material obtained by the oxidation of graphene and bearing numerous oxygen-containing functional groups such as hydroxyl, epoxide, and carboxyl groups on its surface.[1] The presence of these functional groups gives GO a highly hydrophilic property, ensuring its stable dispersion in aqueous media.[2] At the same time, GO serves as a convenient platform for the modification of various organic and inorganic molecules by covalent or non-covalent means, thanks to its rich surface chemistry.[3] The high specific surface area, structural flexibility, and chemical functionalization capabilities of GO make it a promising material widely used in the fields of catalysis, energy systems, and materials science.[4]

This study provides an integrated experimental and computational demonstration of a covalently engineered amine–graphene oxide (AM–GO) interface that acts as a molecular regulator of palladium organization and electronic behaviour rather than merely serving as a passive metal-binding support. Pd@GOA was prepared through sequential covalent grafting of AM onto GO, coordination of palladium species, and controlled partial reduction. The resulting dual-anchoring architecture combines stable covalent C–N linkages with multidentate Pd–N coordination, thereby coupling palladium immobilization and nanoscale dispersion with mixed-valence stabilization and modulation of the electronic structure of GO.

The stepwise formation of the hybrid interface was experimentally verified using XRD, FT-IR, UV–Vis spectroscopy, TEM, EDX mapping, and XPS. Microscopic and elemental analyses demonstrated the broad distribution of Pd-containing nanostructures across the functionalized GO surface. XPS revealed the coexistence of Pd(0) and Pd(II), with a predominantly Pd(II)-rich interfacial state, while changes in the N 1s region supported the involvement of TREN nitrogen centres in Pd coordination. Density functional theory provided molecular-level insight into the structural and electronic consequences of interface formation. The calculations confirmed the feasibility of both covalent AM attachment and Pd–N coordination and revealed pronounced charge redistribution following incorporation of the AM–Pd unit. Importantly, the calculated electronic descriptors showed a substantial narrowing of the frontier-state energy separation accompanied by a marked increase in global softness. These changes indicate enhanced electronic responsiveness and demonstrate that AM–Pd integration actively modifies the electronic environment of GO. The computational findings therefore support the experimentally observed stabilization of the mixed-valence palladium interface and establish a direct relationship between molecular coordination, electronic-state modulation, and material function.

As a proof of function, Pd@GOA promoted aryl–aryl, aryl–heteroaryl, and heteroaryl–heteroaryl Suzuki–Miyaura cross-couplings with consistently high product yields and maintained its catalytic performance over repeated reuse cycles. Overall, the findings establish covalent AM functionalization as a molecular-interface engineering strategy for simultaneously controlling palladium dispersion, oxidation-state distribution, and the electronic properties of graphene oxide.

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Strategy-first synthesis planning for complex natural products

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The total synthesis of complex natural products is one of the most demanding tasks in organic chemistry. Existing computational tools score poorly on these targets. This failure is driven by the inaccessibility of the desired disconnections and the lack of a coherent multistep strategy. Patent-trained planners struggle to navigate environments outside of recurring medicinal chemistry motifs. This results in a tendency to fall into functional group interconversion and protection-deprotection cycles rather than decomplexifying the core skeleton [1].

Large language models have shown great advances in chemistry. Their capabilities now include strong correlation with human judgment in synthesis evaluation and strategic reasoning [2]. However, their direct utility in autonomous synthesis planning has not been fully demonstrated at scale. Existing model implementations mostly select within reaction spaces already mapped out by conventional tree searches [3]. They remain tethered to historical patent libraries and cannot easily instantiate the rare, bespoke chemistry required for complex ring formations.

We introduce a new framework, SynthEx, which solves 701 of 1,098 complex natural products from the NP Atlas benchmark, drawing from a unique reaction space. SynthEx removes the patent reaction distribution constraint by directly generating candidate reactions with a language model. Rather than letting a route emerge passively from a node search, the system commits to a high-level strategy built around a key disconnection. It expresses each disconnection as an ordered list of atom-level graph edits, known as ReactionJSON, meaning the model writes the chemistry instead of selecting it from a catalog. A designated loop of Critic and Editor agents then evaluates and repairs problematic steps iteratively without abandoning the core strategy.

The chemistry proposed by SynthEx is measurably different from existing state of the art models, with carbon-carbon bond formation and ring construction make up a significantly higher share of its reaction space [4]. In a blinded assessment, ten expert synthetic chemists rated SynthEx key steps against those from published literature routes. They found no detectable difference from published human work in terms of feasibility, elegance, and overall quality. The system successfully reconstructed the logic of expert routes and independently selected complex cascade disconnections that parallel actual laboratory efforts.

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Synthesis of new Push-Pull type monomers and study of their polymerization

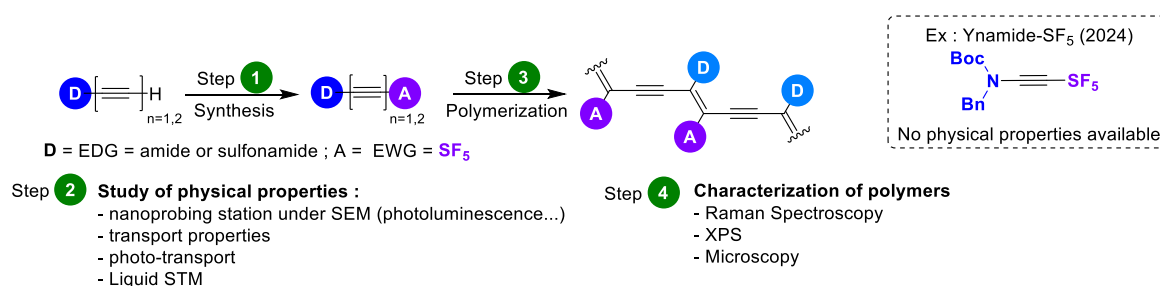
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Push-pull molecules are organic compounds featuring both an electron-donating group (EDG) and an electron-withdrawing group (EWG), connected by a π -linker. This class of molecules has attracted significant interest in materials science, particularly in applications such as organic photovoltaic cells and liquid crystals, due to their unique physical properties [1]. A key advantage is the tunability of their properties: by modifying any of the three components (EDG, EWG, or π -linker), their characteristics can be finely adjusted. Among potential EWGs, the pentafluorosulfanyl (SF_5) exhibits a strong electron-withdrawing effect between a trifluoromethyl and a nitro group [2]. This makes SF_5 a promising candidate for the design of new push-pull systems [3]. While examples of push-pull molecules incorporating SF_5 exist, the SF_5 group is typically positioned on aromatic rings, as the synthesis of SF_5 -alkynes or SF_5 -alkenes remains challenging. To date, only one study has reported the synthesis of push-pull ynamides with SF_5 on a triple bond, though the resulting product was not physically characterized [4]. In this work, we propose the synthesis of novel SF_5 -based push-pull molecules with a triple-bond linker. Following their synthesis, we aim to investigate their physical properties and explore polymerization strategies to obtain push-pull polymers. These polymers will be thoroughly analyzed and characterized using various methods.



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Reaction agnostic enumeration

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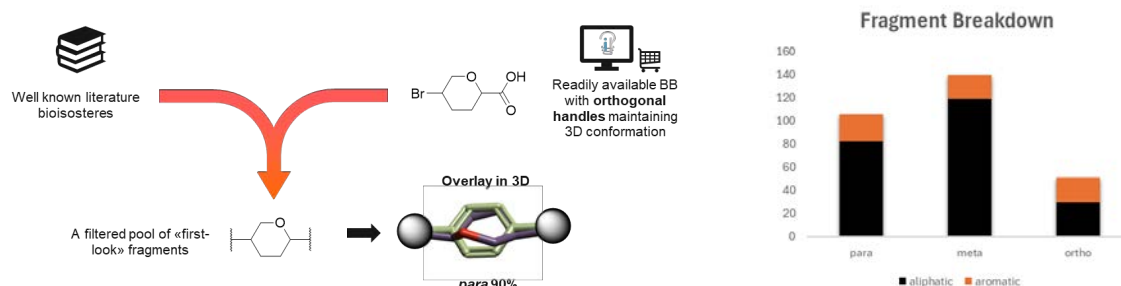
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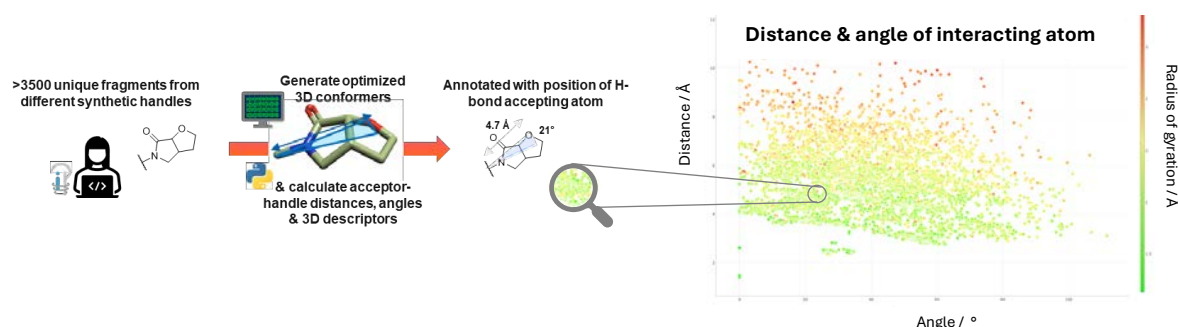
The increasing integration of digital tools into medicinal chemistry positions *in silico* design as a key driver of efficiency across the DMTA cycle.

Medicinal chemists use several recurring strategies to develop a compound from hit to lead. These include isostere replacements/scaffold morphs, to improve properties e.g., by increasing 3D character, as well as engineering in targeted interactions to gain potency.

Increasing 3D character remains challenging in building block-driven design: standard enumeration is largely confined to 2D searches, while generative approaches often yield black-box designs that are difficult to prioritize for synthetic accessibility. Although phenyl bioisosteres are well documented, many alternative motifs accessible from readily available building blocks remain unexplored, while literature examples are often not directly tractable within enumerative workflows. To address this, we sought efficient ways to visualize this well-documented space without repetitive manual design, while uncovering new bioisosteres from modern building block collections.



Analogously, designing new interactions from a given scaffold is time-consuming and computationally expensive if all possible building blocks must be exhaustively evaluated. We therefore envisioned a strategy to rapidly refine readily-available building blocks based on the 3D position of their interacting atom. These compact, filterable sets dramatically reduce the search space, accelerating design and shortening key phases of the DMTA cycle.



The democratization of digital tools enables synthetic chemists to design in parallel while deliberately constraining exploration to synthetically accessible space. Reaction agnostic enumeration extends design beyond standard libraries, expanding chemical space beyond predefined building block functionalities while retaining synthetic feasibility. This enables broader exploration of scaffolds and series without the time penalty associated processing, filtering and synthesizing from large generative datasets.

BENZOXAZINE DERIVATIVES AS HIGH-PERFORMANCE BUILDING BLOCKS FOR VOLUMETRIC 3D PRINTING OF REPROCESSABLE THERMOSET

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3D-printing is widely used to polymerize resins into thermosets with complex shapes or geometries. Yet, most of the resins printed have moderate mechanical or thermal performances and are non-recyclable or non-recycled.[1,2] Since the late 90s, benzoxazine thermosets have been proven to significantly enhance the performances of the resins through thermal cure. They are notorious for their excellent thermal stability, strong mechanical properties, low-curing shrinkage and molecular design flexibility, making them ideal for 3D-printable resins. Lastly, as a tertiary amine is generated during the thermal cure, it can act as a catalyst for transesterification reactions, thereby enabling the reprocessing of the material without the need of any external catalyst.[3,4]

In this work, we synthesized a series of acrylated benzoxazine monomers and incorporated them in a photocurable resin suitable for volumetric printing. Following thermal post-curing and ring-opening polymerization of the benzoxazine moieties, the 3D printed objects formed a highly crosslinked network, with glass transition and thermal stability increased by nearly 100°C. The efficiency of the transesterification reactions was evaluated by DMA through relaxation time measurements, while the reprocessing of the printed thermosets was demonstrated by recasting the ground samples via press molding.

Overall, this work demonstrates the potential of benzoxazine derivatives as high-performance building blocks for additive manufacturing, effectively combining enhanced materials properties with improved sustainability.

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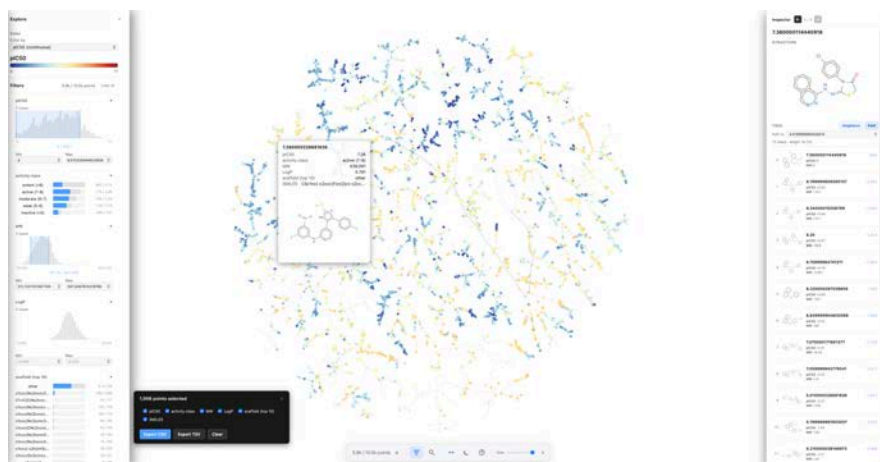
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From Proteins and Molecules to Cats and Dogs: Visualization as Scalable Minimum Spanning Trees

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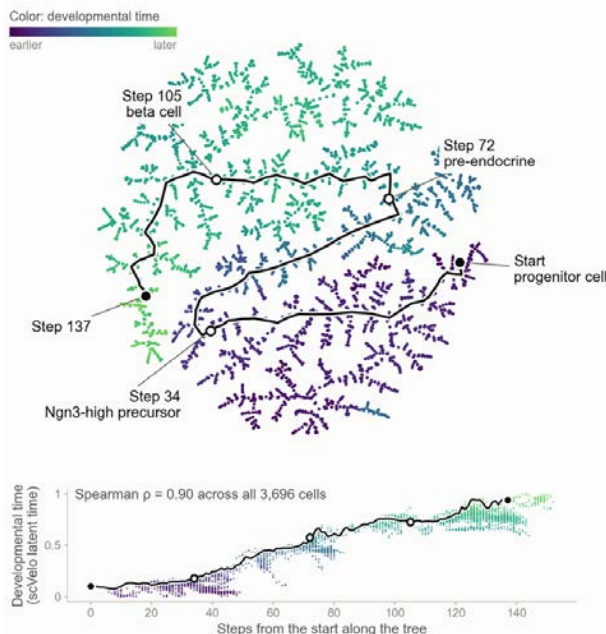
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Here we present TMAP2 for visualizing large and complex datasets as minimum spanning trees. Each point is connected through real nearest-neighbor relationships, so the map can be explored as a network of meaningful paths. This makes it possible not only to see clusters, but to identify relationships across the data. A map of data should not only show where things are. It should also show how one thing is connected to the next. TMAP2 was built for this problem in chemistry. Large molecular libraries contain thousands or millions of compounds, and chemists often want to see more than clusters. They want to follow chemical series, find bridges between scaffolds and understand how one region of chemical space connects to another. TMAP2 turns those relationships into a tree: each compound is connected through nearest-neighbor links, so the map can be searched, filtered, and followed like a route through chemical space. It builds a readable structure, where each edge has a meaning and each path tells a story. The question then becomes which story you want to tell.

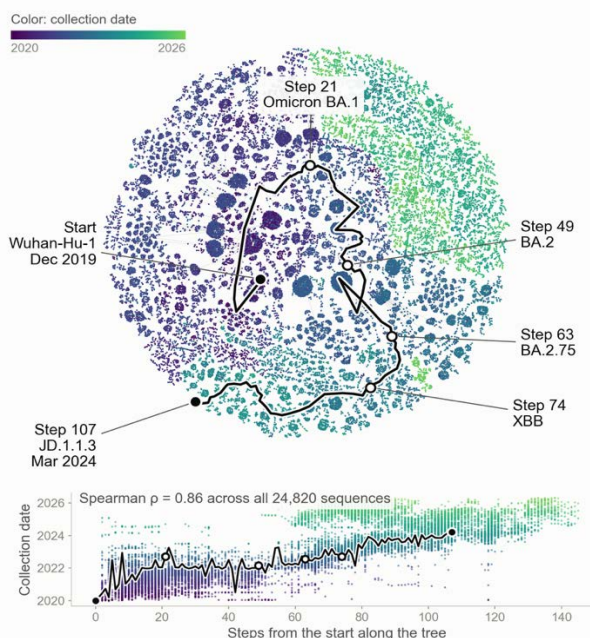


TMAP2 can also recover stories that are not given to the algorithm. We built a tree from SARS-CoV-2 spike protein sequences using only the sequence content. The method was not told when each virus was collected. It only compared sequences by similarity and connected them through nearest-neighbor relationships. Yet when we count the number of tree steps from the original Wuhan-Hu-1 sequence (i.e. how far in the tree they are), the map follows the real calendar history of the pandemic. Early variants stay close to the root, while later variants move farther away along the tree. This shows why topology matters. For evolving systems, developing cells, chemical series, or image collections, those paths can become simple, readable stories.

The tree path from a progenitor cell passes through each stage of pancreatic development in order and ends at a beta cell.



The tree is built from spike sequences alone. Its path from Wuhan-Hu-1 still passes the Omicron variants in the order they emerged.



How do I optimize a reaction when data is scarce and experiments costly?

Transferable enantioselectivity models from sparse datasets

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We have developed a computational strategy to predict the selectivity of mechanistically complex reactions and identify promising catalysts for unseen transformations using only sparse data for training. The key methodological advancement consisted in a workflow to automatically generate, optimize, and featurize transition state geometries at a fraction of the cost of DFT computations. We used these inexpensive parameters to train machine learning models of enantioselectivity, enabling high-throughput screening. We have demonstrated the utility of this approach in the context of asymmetric nickel-catalyzed cross-electrophile coupling reactions, an emerging field due to its ability to construct enantioenriched molecules in a single step from widely available starting materials. Specifically, we have addressed challenges associated with sparse data *i.e.*, where limited information on substrate-catalyst interactions is available. The features extracted from the low-cost TSs explicitly capture these interactions, and thus allowed us to train regression models transferable to unseen classes of both substrates and ligands. We successfully tackled two problems frequently encountered in synthesizing enantioenriched products according to published procedures: (1) identifying a better-performing ligand for a product in a reaction's scope previously reported in low enantioselectivity, and (2) "warm starting" the optimization of a transformation involving a new coupling partner. In both cases, we found the ML models trained on literature data involving different but structurally related ligands and substrates to afford accurate predictions on out-of-sample reactions, allowing us to identify promising catalysts within a limited number of experiments, significantly saving time and resources.

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Transition metal-catalyzed regio- and stereoselective hydrometallation of polarized alkynes

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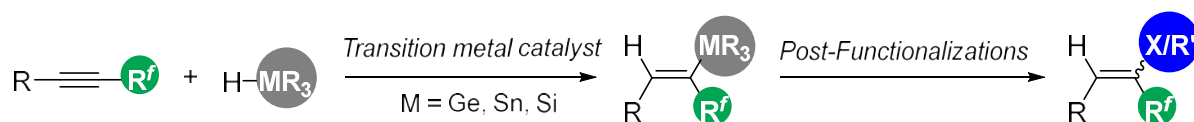
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Nowadays, fluorine chemistry plays a crucial role in medicine and agriculture with nearly 20% of marketed drugs and 50% of agrochemicals containing at least one fluorine atom.¹ Our group has a long-lasting interest in the synthesis and the use of fluorinated alkynes for the design of complex molecules. They are modular organic building blocks where the electron-withdrawing properties of fluorinated motifs R^f strongly polarize the triple bond.

Transition metal-catalyzed hydrometallation of triple bonds is a useful technic to access metallated-olefins as valuable building block for further functionalization such as cross coupling. Unfortunately, this reaction usually suffers from very low selectivity and/or is biased by the substrate making this reaction poorly attractive. Our group developed several strategies to performed regiodivergent hydrometallation of polarized alkynes, mainly controlled by the reaction conditions but also thanks to the polarization of the alkyne.² On this poster are presented efficient methods to perform fully regio- and stereoselective hydrometallation of fluorinated alkynes with crystallogens (Ge, Sn, Si) together with further post-functionalizations.



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RXNMapperv2: updated validation and evaluation on expanded chemical space

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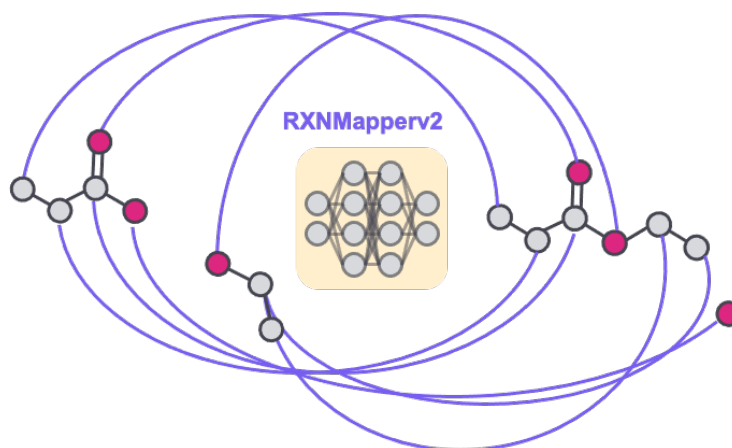
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Atom-to-atom mapping (AAM) assigns reactant atoms to product atoms and is fundamental for reaction classification, template extraction, and synthesis planning. RXNMapper derives AAM from the attention of a Transformer model trained by masked language modeling on unmapped reaction SMILES. However,

its original model selection relied on USPTO-50K, a validation set later shown to contain erroneous mappings. Here we revisit RXNMapper using a curated validation set of 4'533 reactions from the dataset Pistachio. We retrained ALBERT-based RXNMapper models on USPTO-full and Pistachio and selected the

best head, layer, and checkpoint on this new validation set. To improve the comparison of AAM algorithms, we developed an evaluation framework that removes ambiguous reference reactions and compares predictions by reaction graph isomorphism rather than direct string matching, avoiding false negatives from inconsistent formats and symmetry-equivalent mappings. Across the golden dataset, Pistachio, and an internal AstraZeneca medicinal chemistry benchmark, the updated models outperform the original RXNMapper and LocalMapper, while rearrangements remain persistent challenges.



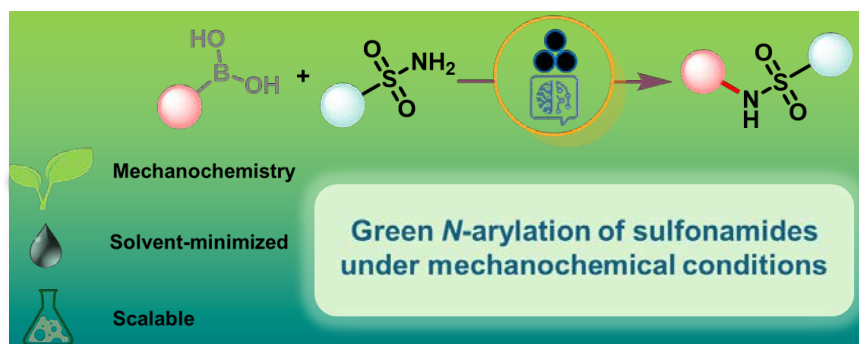
Mechanochemically Accelerated *N*-Arylation: A Scalable and Solvent-Minimized Approach Bypassing Friction Sensitive Reagents

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We report a comprehensive mechanochemical strategy for the solvent-minimized *N*-arylation of sulfonamides via C-N coupling, using commercially available copper powder as the catalyst and water as a green LAG additive. Inspired by the limitations of traditional solution-phase protocols-such as substrate dependency, over arylation, and poor sustainability, we developed a scalable, efficient and eco-compatible protocol under ball-milling conditions.^[1]



Initial screening revealed the high thermal reactivity of *masked amine* reagent, prompting a shift toward primary sulfonamides as safer and more robust nitrogen nucleophiles.^[2] The protocol tolerated a wide range of aryl, heteroaryl and halogenated boronic acids, affording moderate to high yields, although alkyl and chelating 8-quinolinyl substrates remain challenging.^[3] Furthermore, data-driven modeling based on molecular descriptors enabled as an exploratory QSAR tool, which guided successful extension to new substrates. The process was readily scaled to gram quantities and applied to late-stage functionalization of sulfonamide-containing bioactive scaffolds,^[4] underscoring its potential as a practical and green synthetic strategy for medicinal and process chemistry applications.^[5]

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Dynamics-Aware Geometric Deep Learning for Protein-Protein and Protein-Ligand Binding Site Prediction

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Proteins are dynamic, but most deep learning methods for protein structure and interaction prediction still treat them as static. This limits accuracy for anything conformation-dependent — IDR/IDP interactions, cryptic pockets, allosteric sites. We address this with three connected projects.

First, DynaRepo¹: a repository of ~450 protein complex and ~270 single-chain MD simulations, totaling over 1,100 μ s. This directly targets the data bottleneck limiting dynamics-aware ML in the field.

Second, DynamicGT², a geometric transformer for protein-protein interaction site prediction. It uses dynamic features, atomic fluctuations, motion correlations, extracted from trajectories, and outperforms static models specifically on flexible and disordered regions.

Third, SIMORGH, extending this to protein-ligand binding site prediction. Unlike DynamicGT, it requires no explicit feature engineering from trajectories: a structure-level equivariant encoder learns representations from individual backbone conformations, and a lightweight consensus-based aggregation module integrates them across the ensemble, with near-linear scaling in protein and ensemble size. SIMORGH matches or exceeds existing methods on standard holo benchmarks, and outperforms them under ligand-free conditions, including on a benchmark of 200+ MD trajectories of cryptic-pocket apo proteins. Together, these results demonstrate that conformational ensembles encode information absent from static structures, and that this information can be learned efficiently. As public MD datasets continue to grow, this approach becomes increasingly practical, and frameworks extend naturally to related tasks such as protein design and binding affinity prediction.

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Synthesis of Pentafluorosulfanylated Quinolines via Modified Pfitzinger Reaction

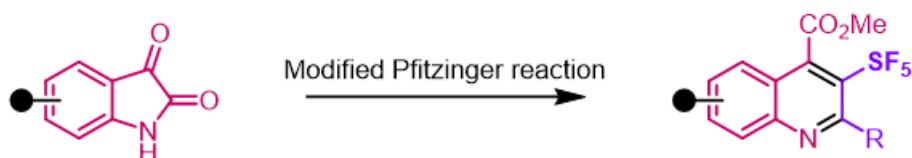
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Nowadays, poly- and per-fluoroalkyl substances (PFAS) undergo increasing criticism and their use is going under strict regulations, restrictions and even bans for some of them. Nevertheless, the properties of the fluorine atom offer advantages that are now indispensable in many applications. One alternative to CF₂X moieties is the pentafluorosulfanyl (SF₅) group. Its unique physicochemical properties are now well-established^[1] while this attractive motif is not considered as a PFAS, leading to applications in medical chemistry, agrochemistry and materials science. Consequently, the synthesis of SF₅-compounds is currently a rapidly growing field.^[2]

To date, the synthesis of pentafluorosulfanylated nitrogen-containing heterocycles remains limited and most often relies on multi-step linear sequences or the use of oxidative fluorination, which is generally incompatible with functional groups. Here, we propose a one-step synthesis of 3-SF₅-quinolines from commercially available isatins via a modified Pfitzinger reaction.^[3]



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Synthesis of Indazoles via intramolecular Inverse Electron Demand

Diels-Alder Reaction of Yne-pyridines

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Inverse electron-demand Diels-Alder cycloadditions (*ihDA*) of azadienes is an efficient method for the rapid elaboration of complex nitrogen containing heterocycles, which are key fragments that are often found in drugs and natural products. In the previous work of our group, it was demonstrated that 2-hydrazonylpyrimidines could be exceptionally activated by trifluoroacetylation and realize Diels-Alder cycloaddition under very mild reaction conditions, providing a large diversity of aza-indazoles. [1-2] Among azadienes, pyridines are known as very poor reactive partners in Diels-Alder reactions, their inherent aromatic stabilization usually requires harsh activation conditions for increasing pyridine reactivity. [3] Therefore, cycloadditions with pyridines is undoubtedly a significant challenge. In this work we report our efforts on the activation of pyridines towards intramolecular inverse electron-demand Diels-Alder reaction followed by retro Diels-Alder reactions (*rDA*) to give access to diversified indazoles.

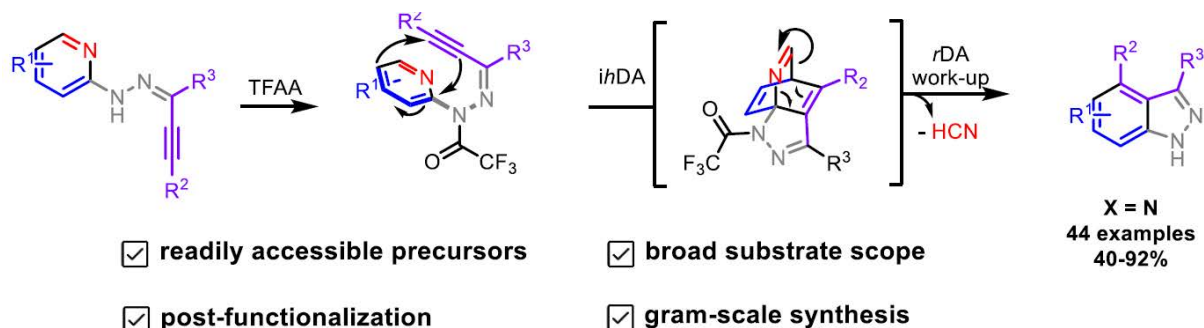


Figure 1 : This work, Diels-Alder of 2-hydrazonylpyridines for the formation of indazoles

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Improving Chemical Impurity Prediction via Bootstrapped Reaction Ensemble

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Predicting chemical impurities is essential for toxicology assessment, intellectual property protection, and understanding reaction mechanisms in pharmaceutical and agrochemical synthesis. We present a method that combines the complementary strengths of a sequence-based model from IBM's RXN platform and a graph-based model from MIT's ASKCOS platform. Our approach incorporates a bootstrapping technique that generates multiple plausible impurity formation pathways from a single reaction, producing a broad candidate set optimized towards high recall. The method is benchmarked on a dataset comprising three complete Syngenta routes for active ingredient candidates totaling 23 synthetic steps with 133 experimentally confirmed impurities—addressing the critical lack of real-world industrial data for impurity prediction.