# Predicting mechanisms and outcomes of complex radical cascades via a hybrid, network-QM-AI approach

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## 1. Introduction

Predicting reaction mechanisms and product distributions remains a central unsolved challenge in chemistry, particularly for multi-step reactions where competing pathways determine outcomes.

Our group recently demonstrated that mechanistic network construction could be used in predicting the outcomes of complex cationic rearrangements [1] and discovering novel multicomponent reactions [2]. However, radical cascades present a more demanding challenge: competing pathways are often separated by only small energetic differences, and selectivity is strictly barrier-controlled. This energetic sensitivity exposes the fundamental limitation of existing approaches — in particular, when tested on even the simplest radical cascade reactions, purely data-driven models including RMechRP [3] and FlowER [4] failed to recover the correct mechanistic pathways within their predictions. At the same time, in this regime, the empirical barrier estimates and extensive hand-crafted heuristics employed in our earlier framework — sufficient for cationic chemistry — were also unable to provide the energetic resolution required for reliable prediction. While quantum chemical calculations provide mechanistic accuracy, their computational cost prevents systematic exploration of large reaction networks.

Faced with these challenges, we developed a quantum chemistry–informed machine learning framework that integrates DFT-derived reaction barriers, rule-based mechanistic enumeration, and microkinetic modelling to enable fast and accurate prediction of complex radical cascade mechanisms and product distributions.

## 2. Quantum Chemistry–Informed Mechanistic Prediction Framework

### *2.1 Barrier Prediction with Mechanistic Features*

We curated database of several hundred radical reaction types and encoded a comprehensive set of mechanistic transformation rules. High-quality DFT transition-state calculations were performed to obtain reaction barriers as training targets.

Machine learning models were then trained using mechanism-specific structural and energetic features derived from conformational searches (Fig. 1a). Random Forest models achieved near–quantum accuracy (≈2 kcal/mol).

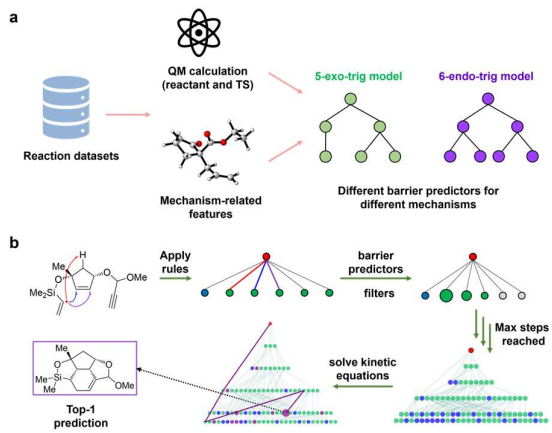


Fig. 1: (a) The workflow for quantum chemistry-informed machine learning. (b) The workflow for radical reaction network prediction. Red dots: initial radicals; green dots: intermediates; blue dots: quenching molecules; grey dots: removed molecules; purple dots: top-10 quenching molecules.

### *2.2 Reaction Network Construction and Kinetic Simulation*

Starting from an initial radical, mechanistic rules were iteratively applied to construct multi-step networks. At each generation, ML-predicted barriers were used to identify kinetically feasible pathways, while physical-organic heuristics pruned unfavourable intermediates, reducing network size by over two orders of magnitude. Predicted barriers were converted into rate constants via the Eyring equation, followed by microkinetic simulation to compute product distributions (Fig. 1b).

The experimentally validated pathways were recovered within the top-10 predictions for

nearly 90% of all multi-step cascades evaluated. To benchmark against existing methods, we tested the ten simplest cases using purely data-driven RMechRP [3] and FlowER [4]. In these cases, our model correctly ranked the ground-truth pathway as the top prediction in every example. By contrast, neither FlowER nor RMechRP were able to retrieve any ground-truth pathway within their predictions.

### *2.3 Case studies*

To evaluate practical applicability, we examined radical cascade reactions that serve as key steps in the synthesis of structurally complex natural products and polycyclic molecules.

For example, in the synthesis of the complex natural product Batrachotoxin [5] (Fig. 2), the framework successfully recovered the literature-reported pathway including rare 4-HAT mechanism and provided a mechanistic rationale for the observed selectivity between competing 5-exo-trig and 6-endo-trig cyclization.

As a further demonstration of its scope, our model could reproduce all the reported major and minor products in the synthesis of polycyclic molecule [6] (Fig. 3). These case studies highlight the model's ability to identify experimentally validated pathways in complex systems while offering interpretable, barrier-based insights into radical reactivity.

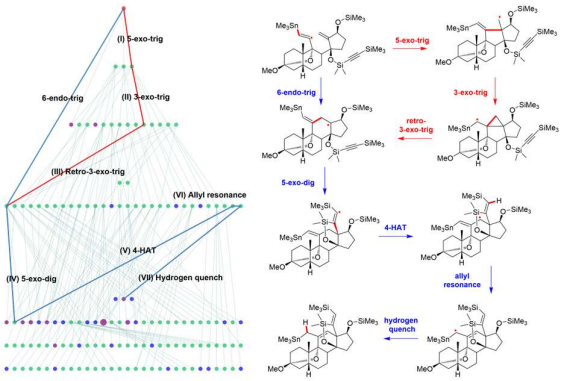


Fig. 2: Predicted radical cascade network for the total synthesis of the natural product batrachotoxin. Red dots: initial radicals; green dots: intermediates; blue dots: quenching molecules; purple dots: top-10 quenching molecules.

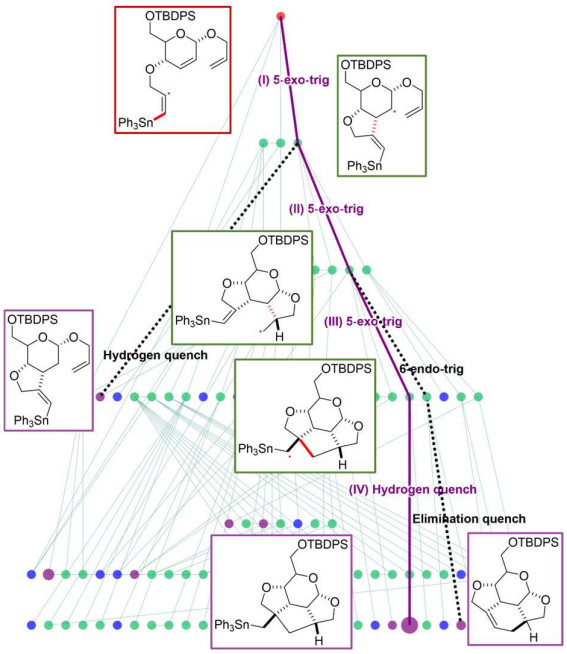


Fig. 3: Predicted radical cascade network for the synthesis of polycyclic molecule. Red dots: initial radicals; green dots: intermediates; blue dots: quenching molecules; purple dots: top-10 quenching molecules.

## References

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