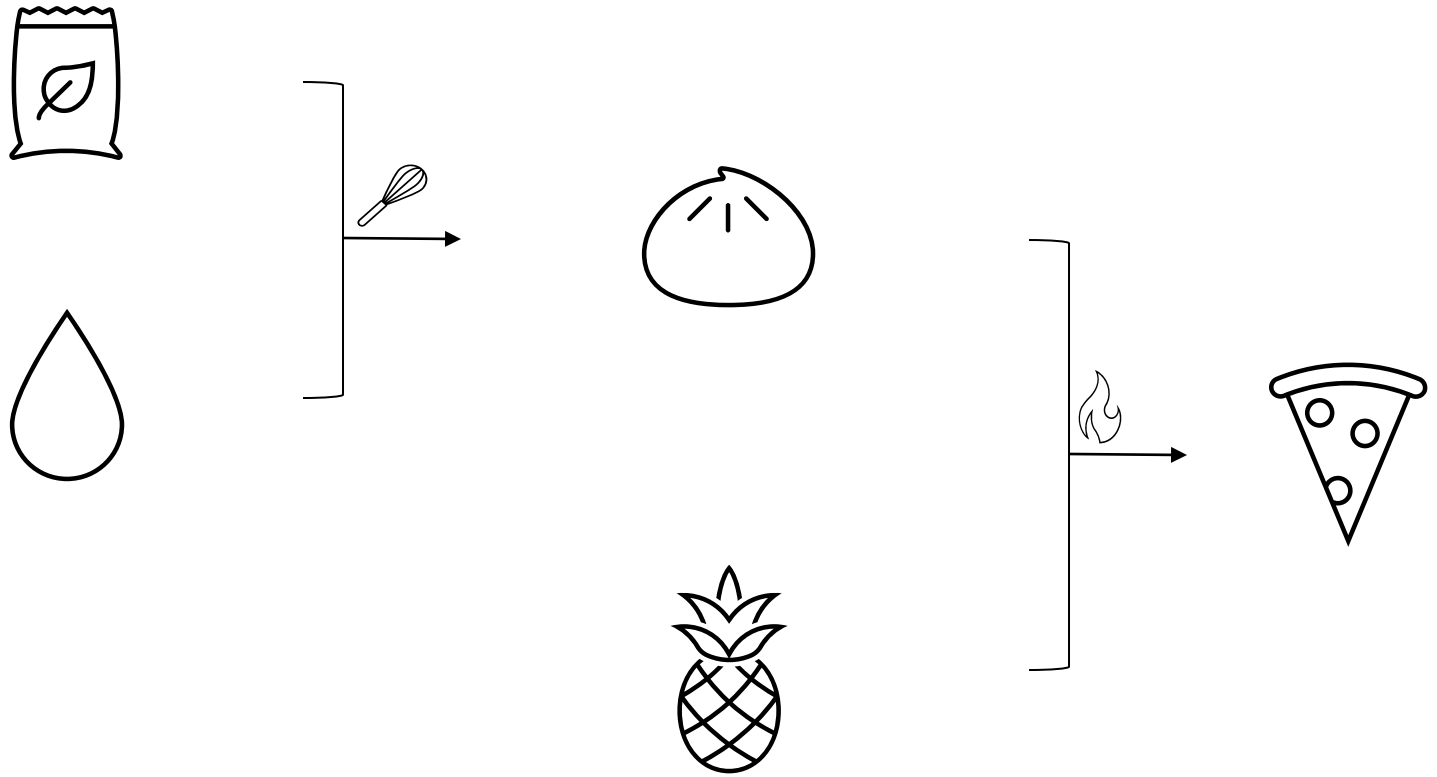
Microsoft

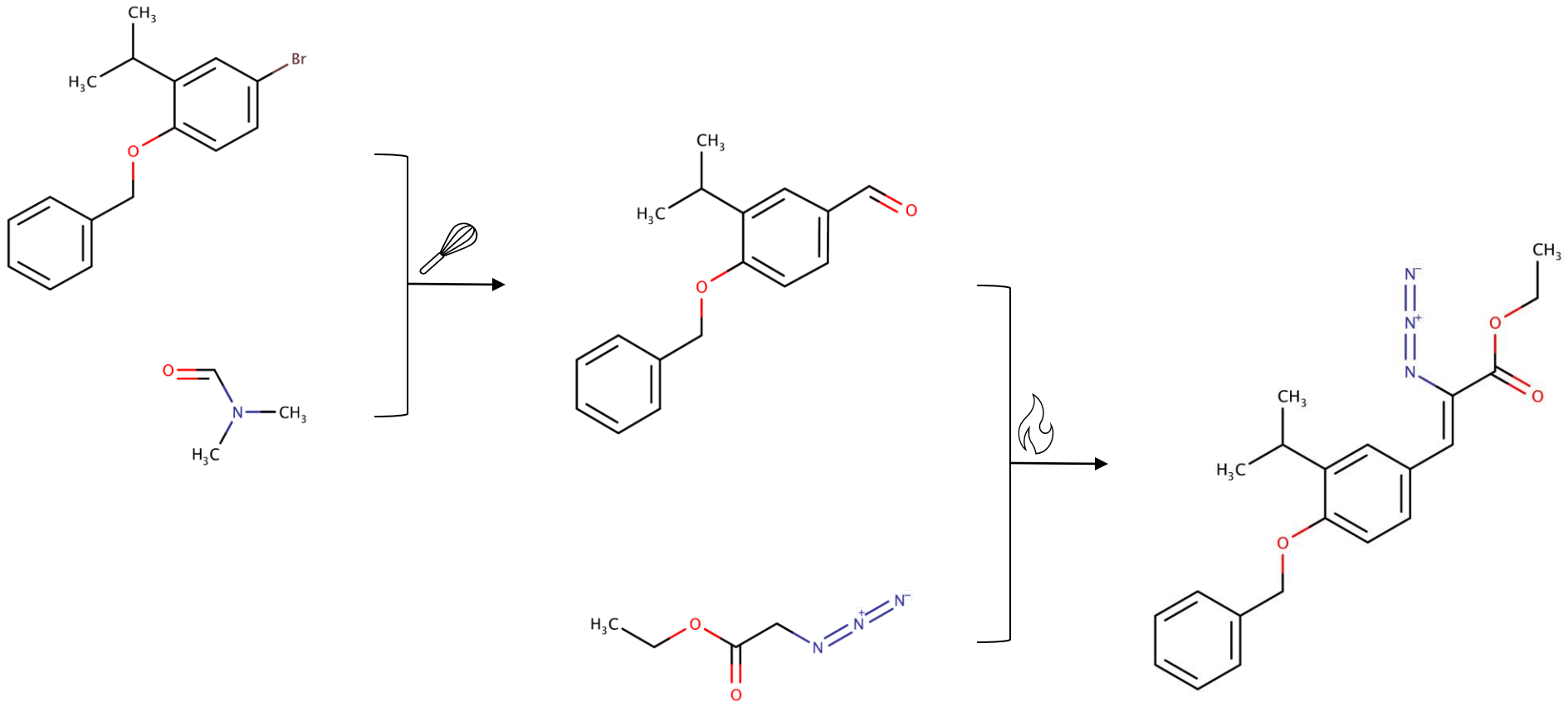
Pushing the boundaries of chemical synthesis with RetroChimera

Krzysztof Maziarz
Principal Researcher @ Microsoft Research AI for Science

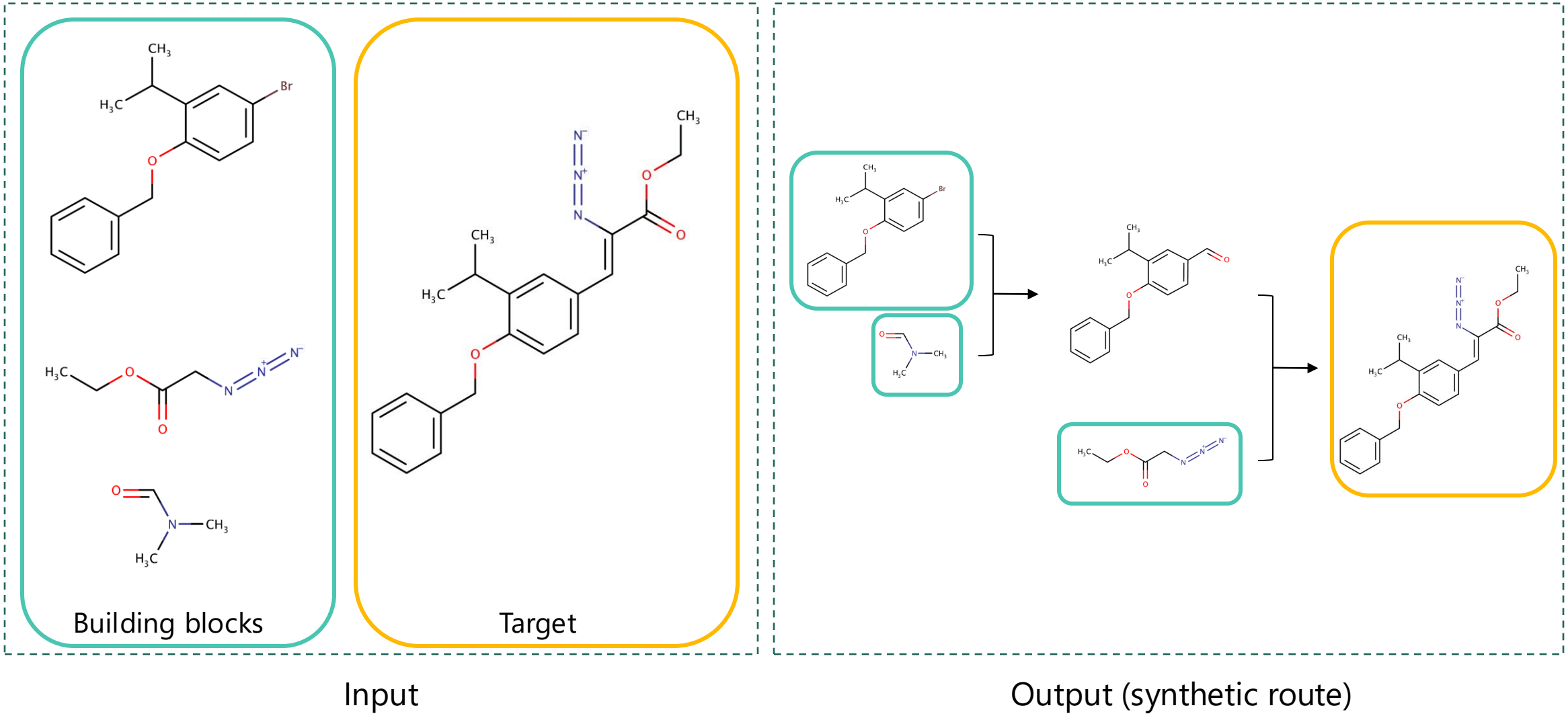
Synthesis: cooking with molecules



Synthesis: cooking with molecules



Synthesis planning



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Demo time

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Why is synthesis planning important?

Small molecules are central to our wellbeing

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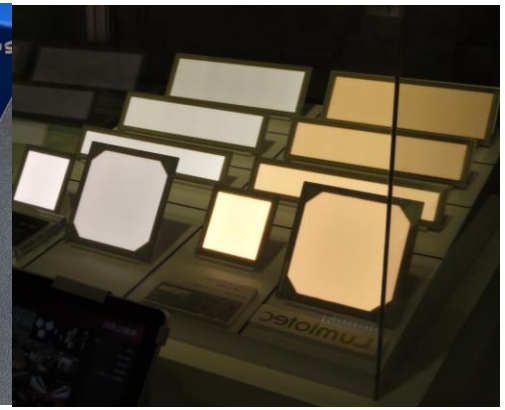
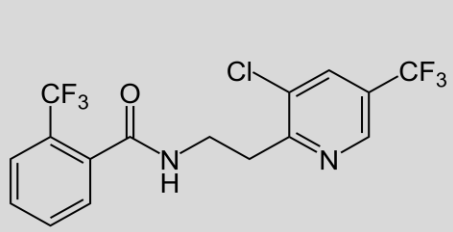
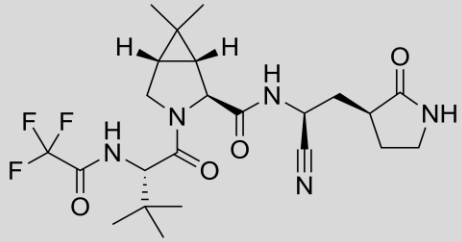
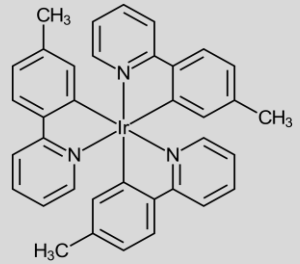




Agrochemicals



Drugs



Materials

Synthesis is a bottleneck in drug discovery

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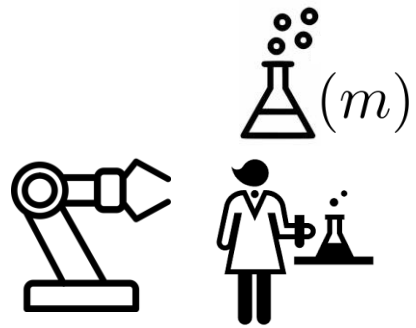
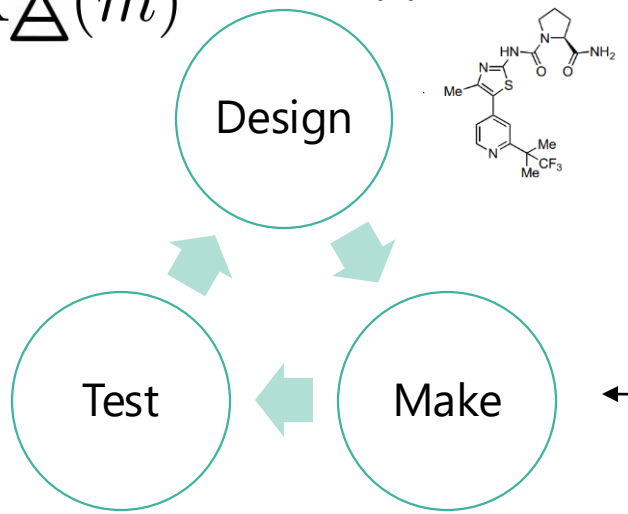
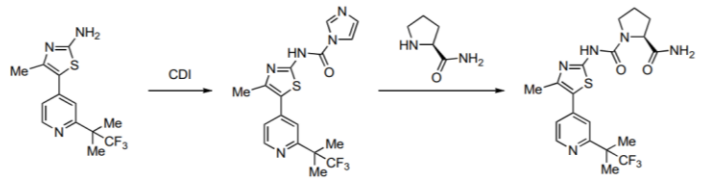
$$\arg\max_{m \in \mathcal{M}} (m) \quad (1)$$





Half of the designs fail here because:

- Synthesis is a multi-step process
- It's time consuming & expensive
- Many reactions fail



(1) Baskin et al *D. Akad. Nauk* SSSR **1989**; Maziarz et al, *ICLR* **2021**; Wu et al. *Nat. Comm.* **2024**

GPS for molecules?

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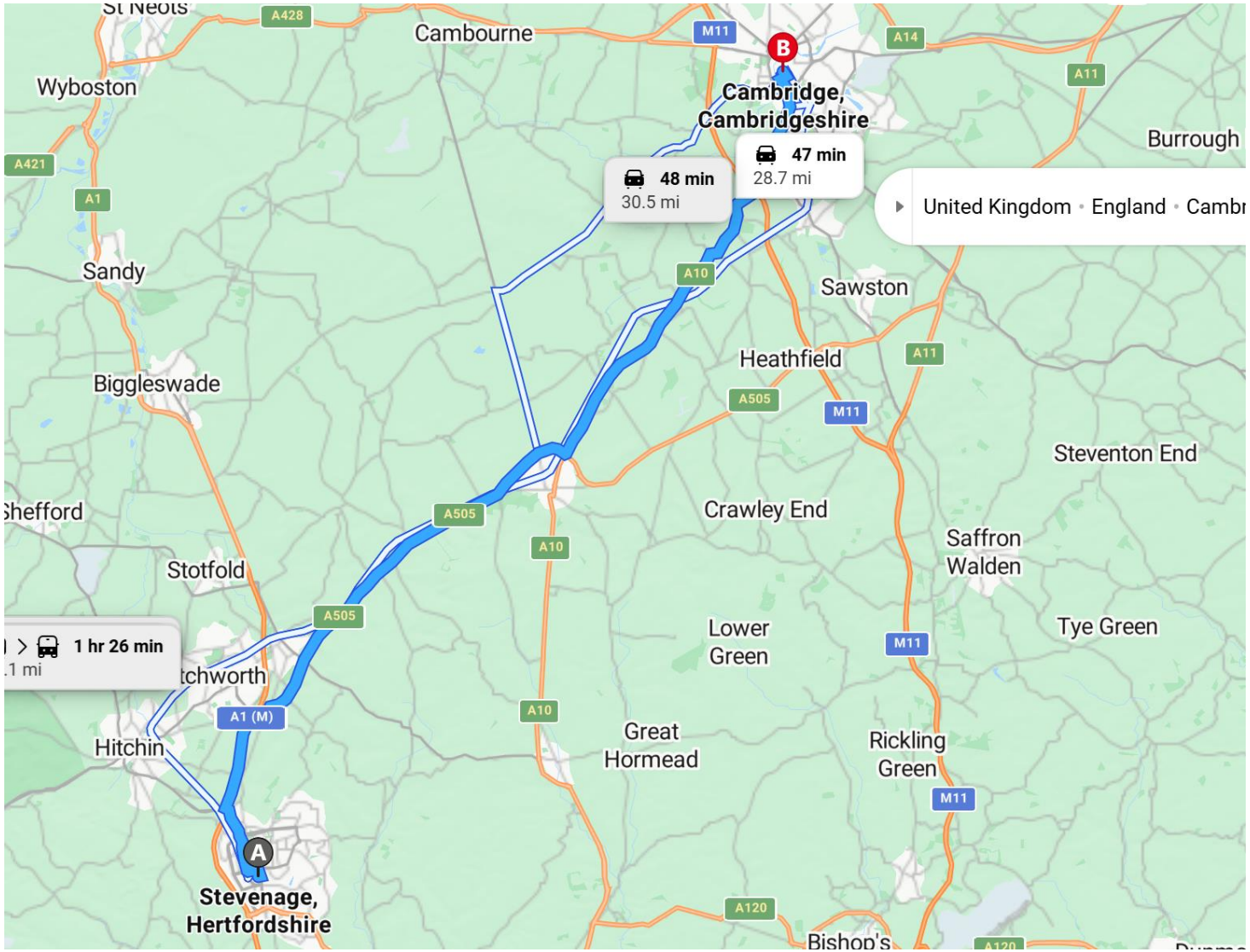

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What kind of modelling is RetroChimera based on?

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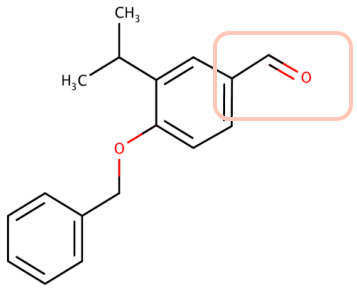
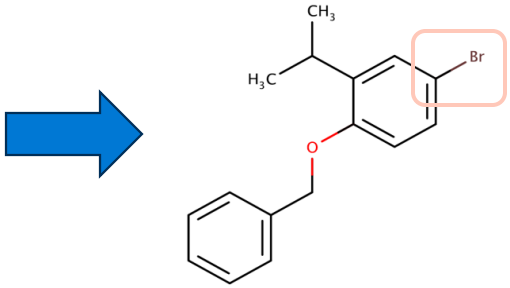
How to model chemical reactions

Input (Product)

Output (Reactants)

Molecular Graph





SMILES
(Graph as Token Sequence)

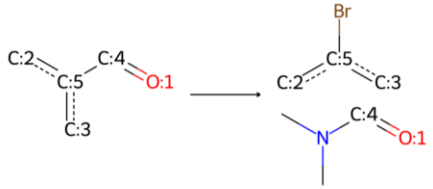
`CC(C)c1cc(C=O)ccc1OCc1ccccc1`

`CN(C)C=O.CC(C)c1cc(Br)ccc1OCc1ccccc1`

Predict Reactants *De Novo*

`CN(C)C=O.CC(C)c1cc(Br)ccc1OCc1ccccc1`

Predict Molecular *Edits*



Applying Edit Template to product yields reactants

Approach #1: end-to-end Transformer

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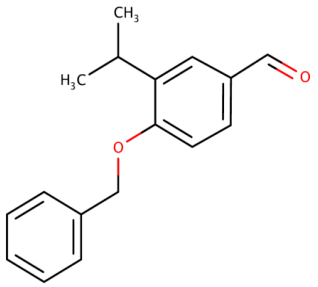
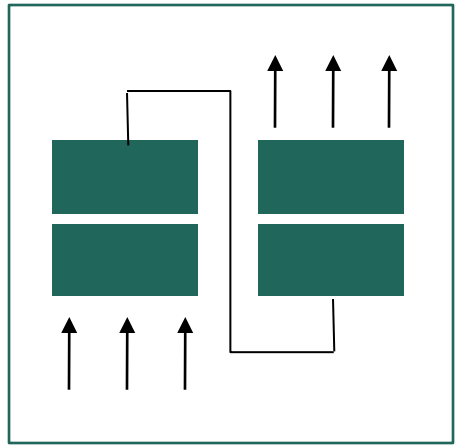
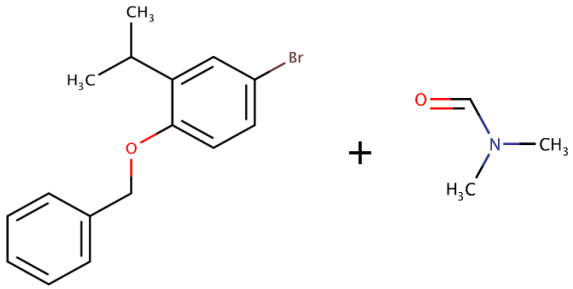


CC(C)C1=CC(C=O)=CC=C1OCC1=CC=CC=C1

Input: Product in SMILES notation



Encoder-Decoder Transformer



CC(C)C1=CC(Br)...

Output: Reactants in SMILES notation

Approach #1: end-to-end Transformer

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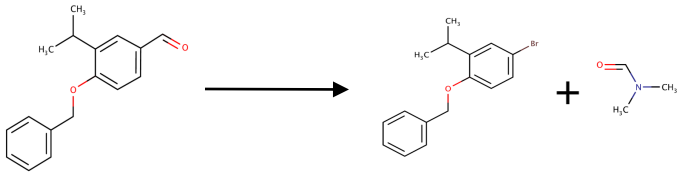
1. R-SMILES alignment and augmentation

Product **Reactants**

Molecular Graph:



1. Canonical SMILES:

CC(C)c1cc(C=O)ccc1OCc1ccccc1 → CC(C)c1cc(Br)ccc1OCc1ccccc1.CN(C)C=O

2. Randomized SMILES:

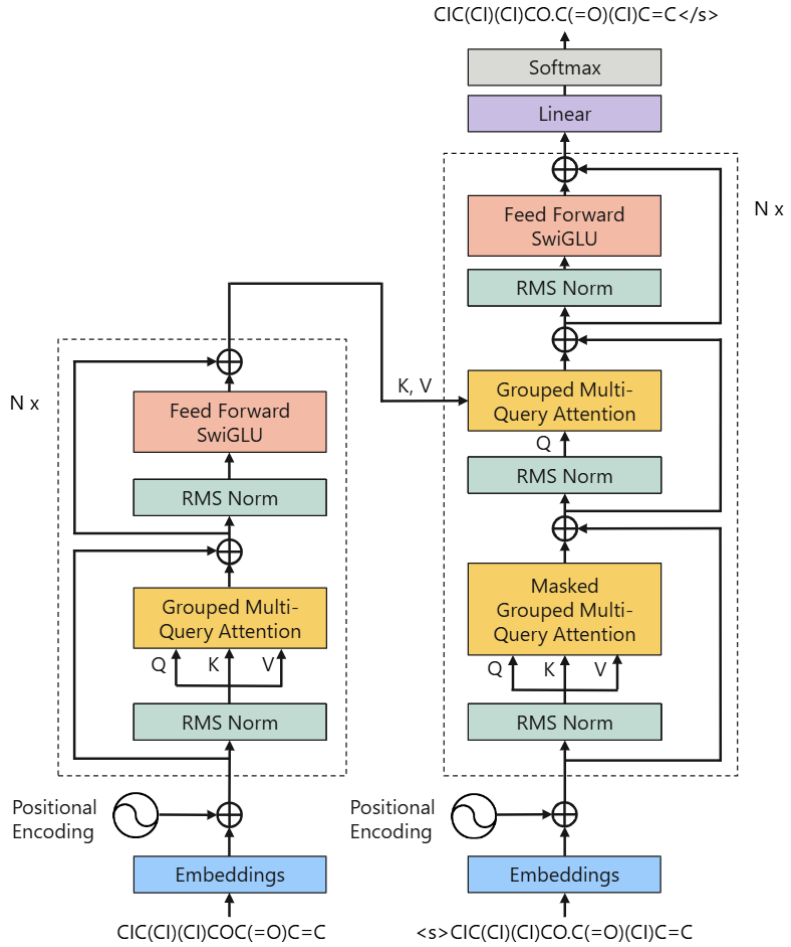
CC(C)c1cc(C=O)ccc1OCc1ccccc1 → CN(C)C=O.c1(C(C)C)c(OCc2ccccc2)ccc(Br)c1
c1ccccc1COc1c(C(C)C)cc(C=O)cc1 → CN(C)C=O.c1(COc2ccc(cc2C(C)C)Br)ccccc1
c1cccc(COc2c(C(C)C)cc(C=O)cc2)c1 → C(C)(C)c1cc(ccc1OCc1ccccc1)Br.CN(C=O)C

3. Root-aligned SMILES (plus N times augmentation):

CC(C)c1cc(C=O)ccc1OCc1ccccc1 → CC(C)c1cc(Br)ccc1OCc1ccccc1.C(=O)N(C)C
c1ccccc1COc1c(C(C)C)cc(C=O)cc1 → c1ccccc1COc1c(C(C)C)cc(Br)cc1.C(=O)N(C)C
c1cccc(COc2c(C(C)C)cc(C=O)cc2)c1 → c1cccc(COc2c(C(C)C)cc(Br)cc2)c1.C(=O)N(C)C

Leverage atom mapping information to reduce edit distance between two sides

2. Model architecture



Approach #1: end-to-end Transformer

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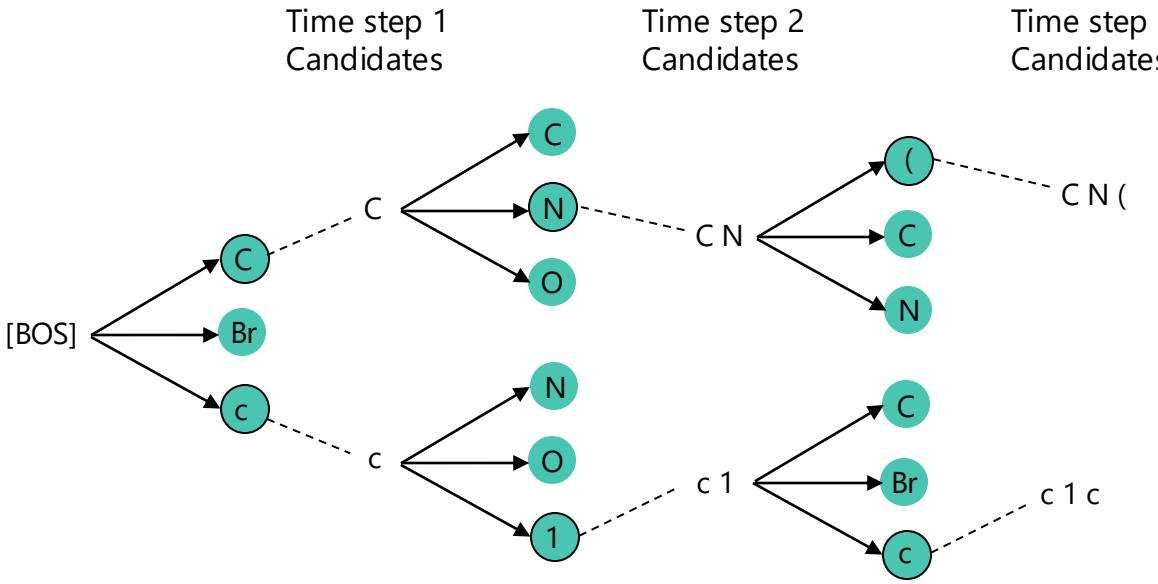
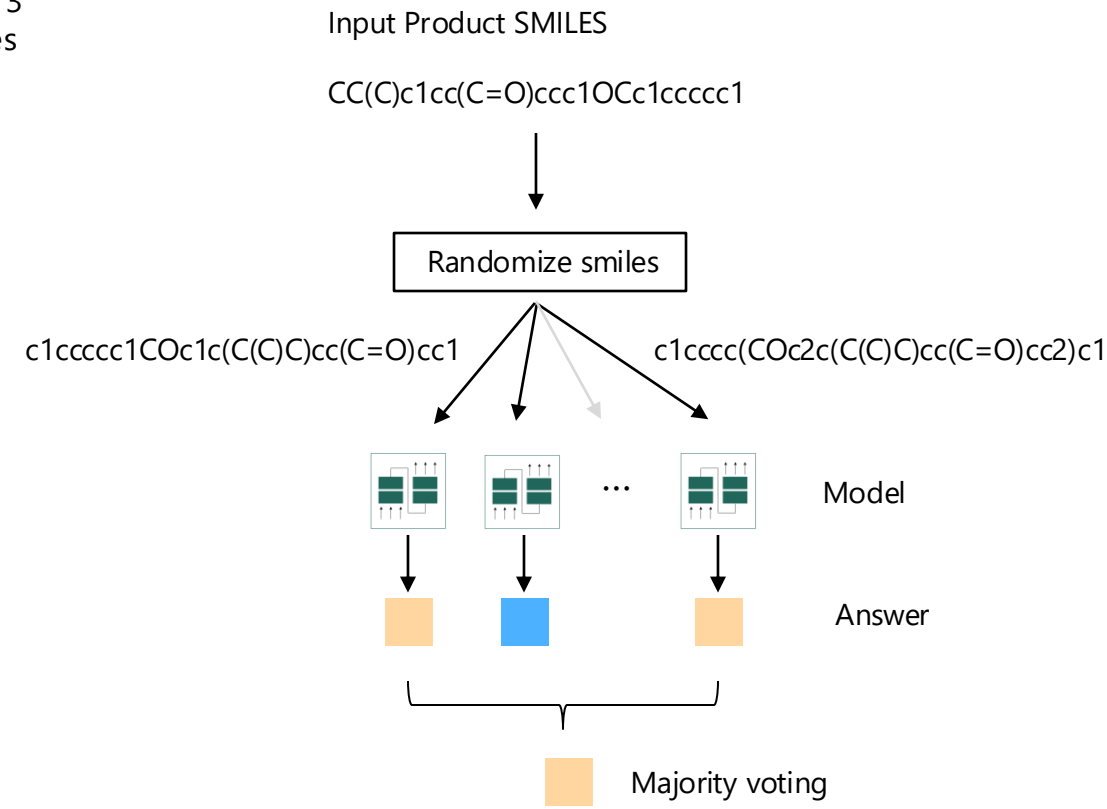
3. Optimized decoding for retrosynthesis prediction



Beam Search Strategy 1 (utilized by OpenNMT): Maintain a pool to save ended sequences during search, search are done until two conditions are met: 1) the pool size = beam size; 2) the top-rated sequence in the beam has lower probability than all candidates in the pool

Beam Search Strategy 2: Keep ended sequences within the beam itself, search are done when each sequence in the beam finishes with the EOS token

4. Test-time augmentation



Approach #2: template-based GNN

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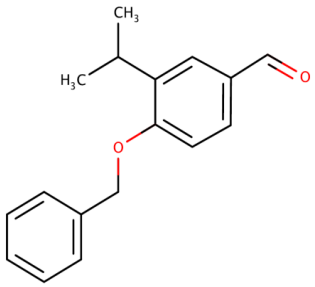
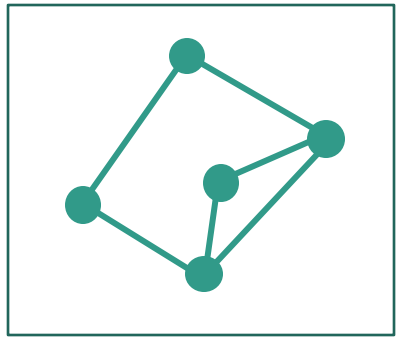
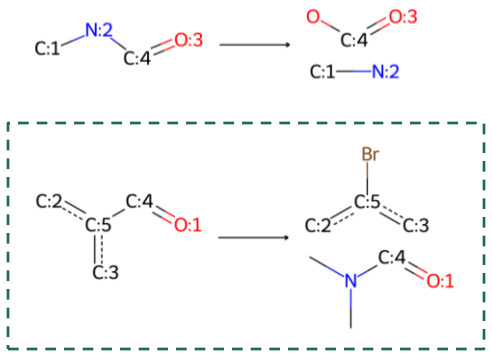
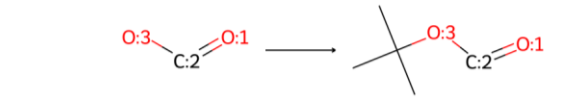


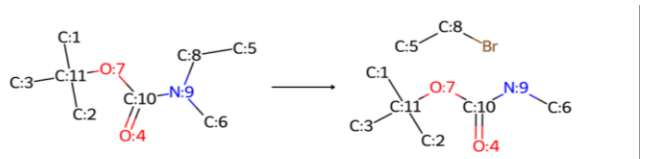


GNN Encoder

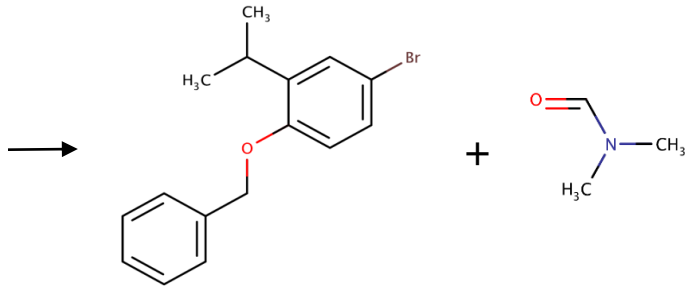
Template (graph rewrite) library







...



Approach #2: template-based GNN

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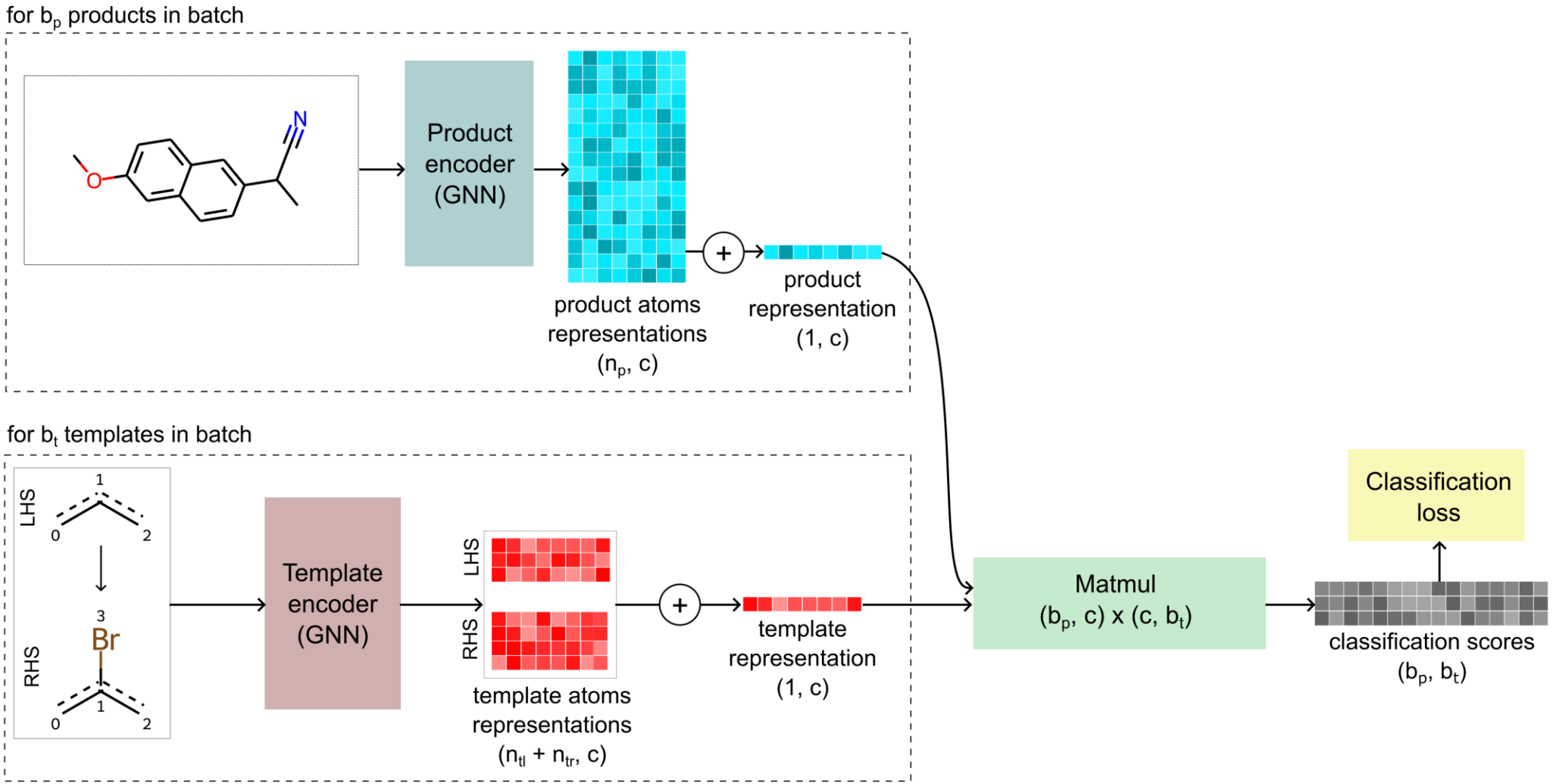

Approach #2: template-based GNN

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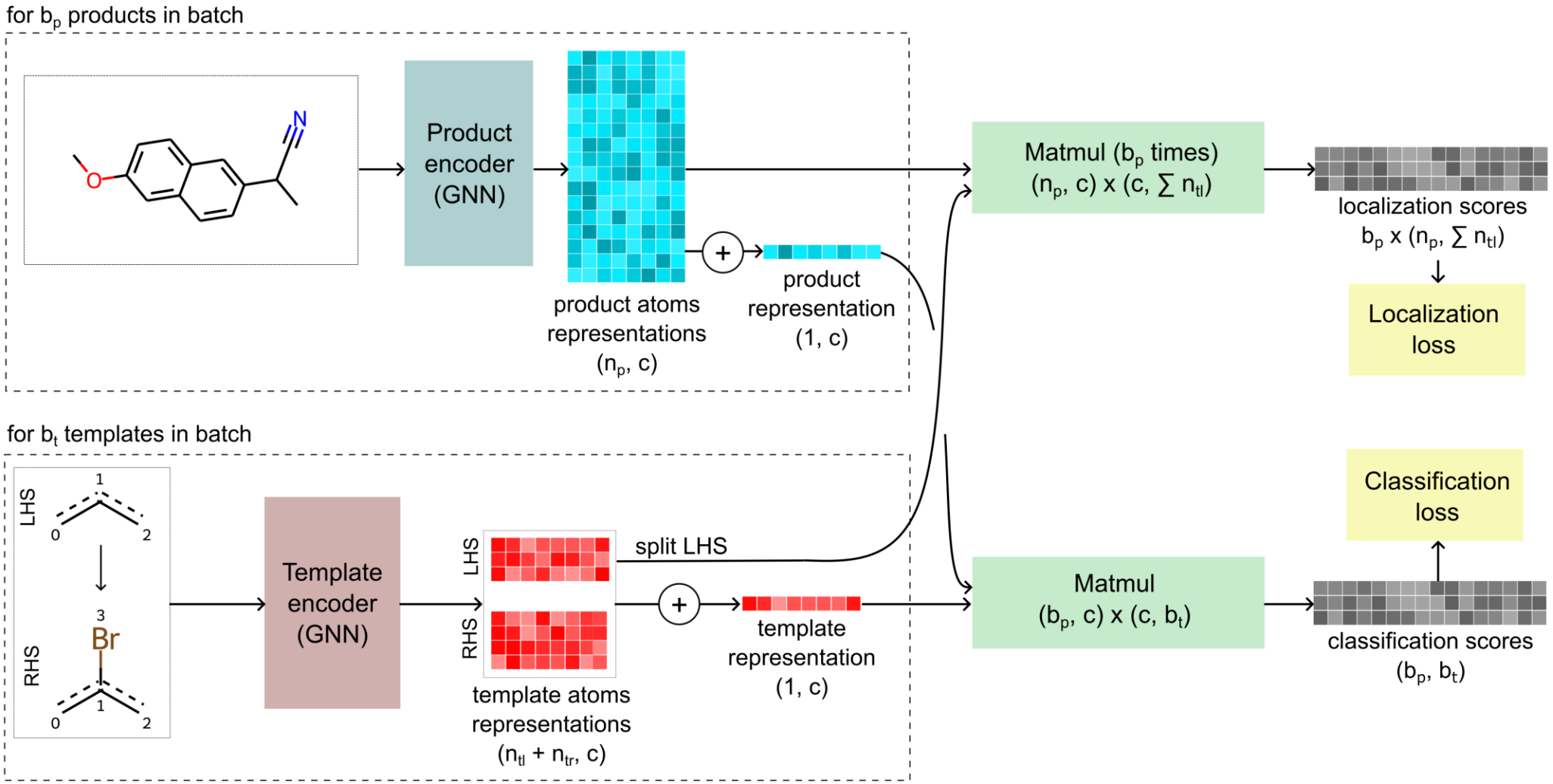

Comparison

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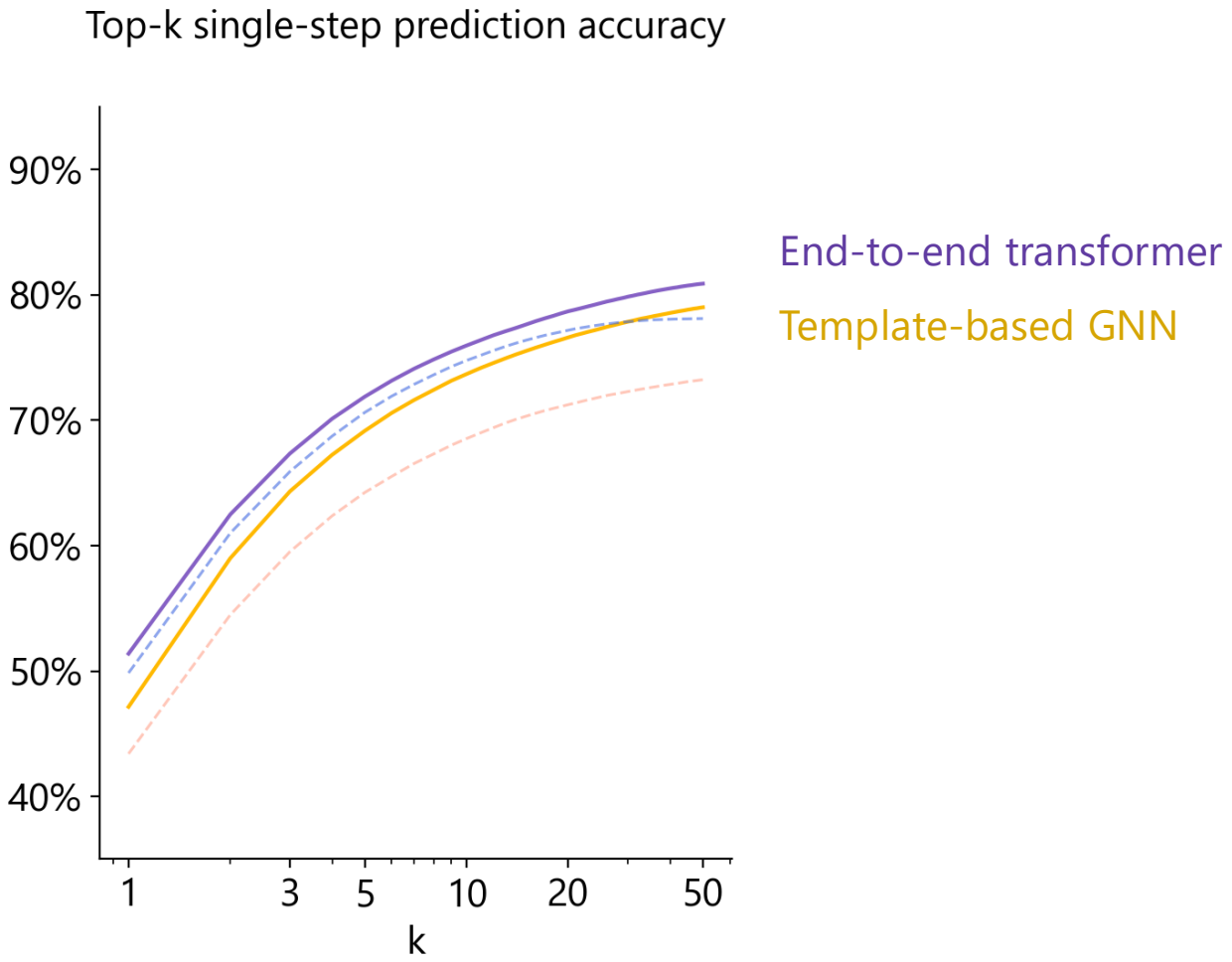

Comparison: trade-offs

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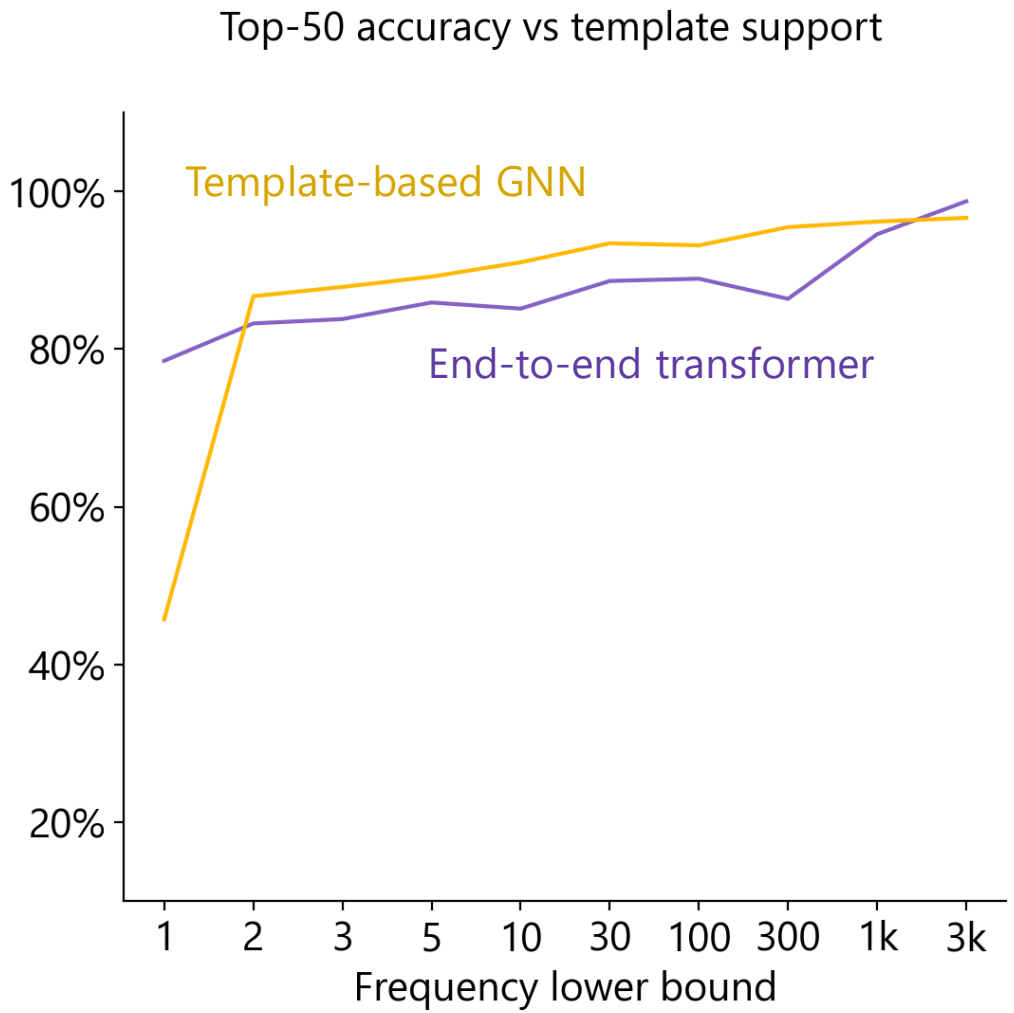

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How does RetroChimera fuse results from its submodels?

Microsoft Research

Learned ensembling

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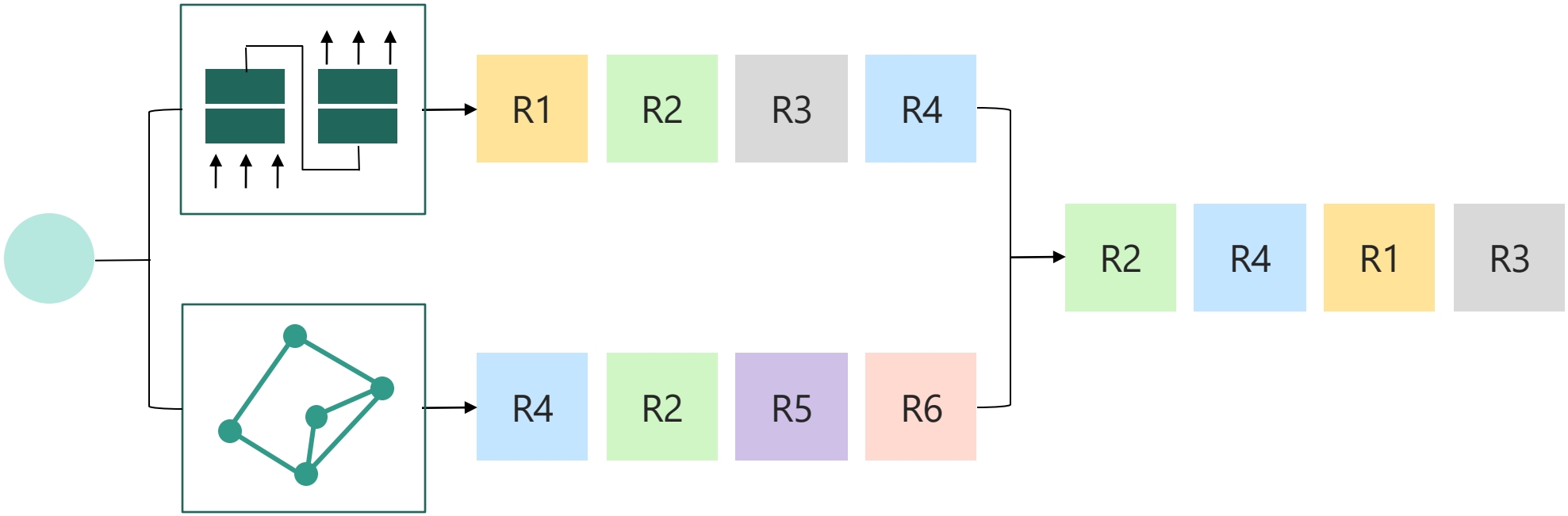

Learned ensembling

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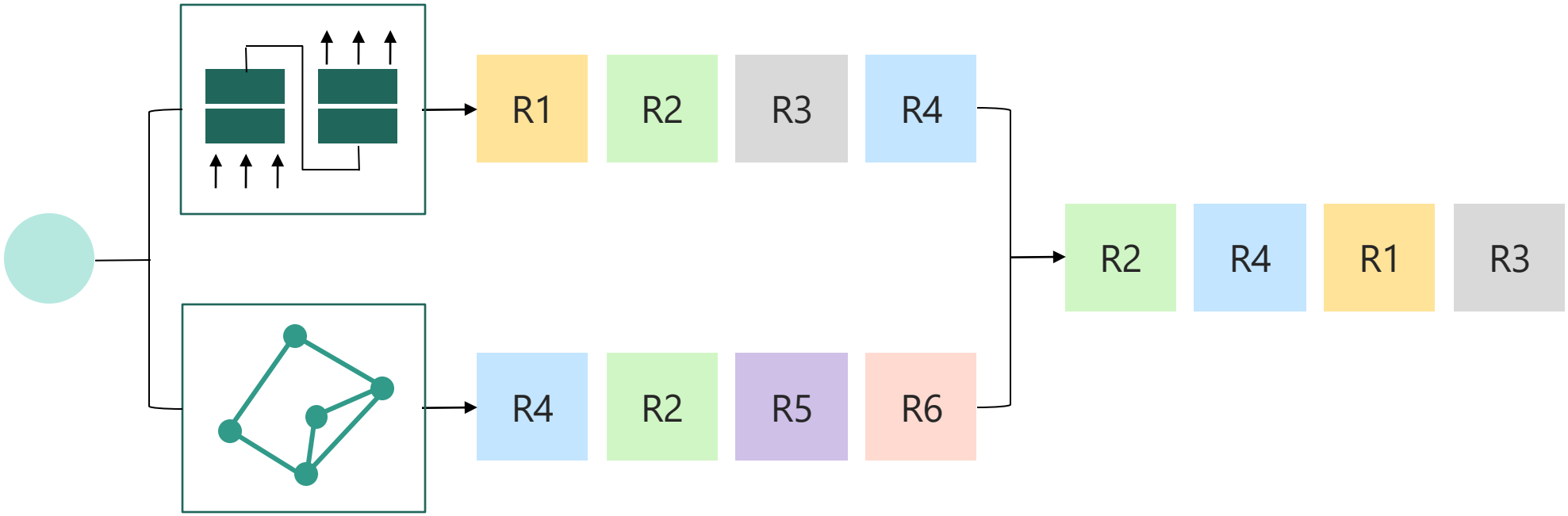

$$\texttt{score}(r) = \sum_{i=1}^{m} \sum_{k=1}^{k_{max}} \mathbb{1}[r = r_{i,k}] \cdot \theta_{i,k}$$

$$\mathcal{L}_{rank}(r^+, r^-) = \sigma\left(\frac{\texttt{score}(r^-) - \texttt{score}(r^+) + \epsilon}{T}\right)$$

RetroChimera's performance

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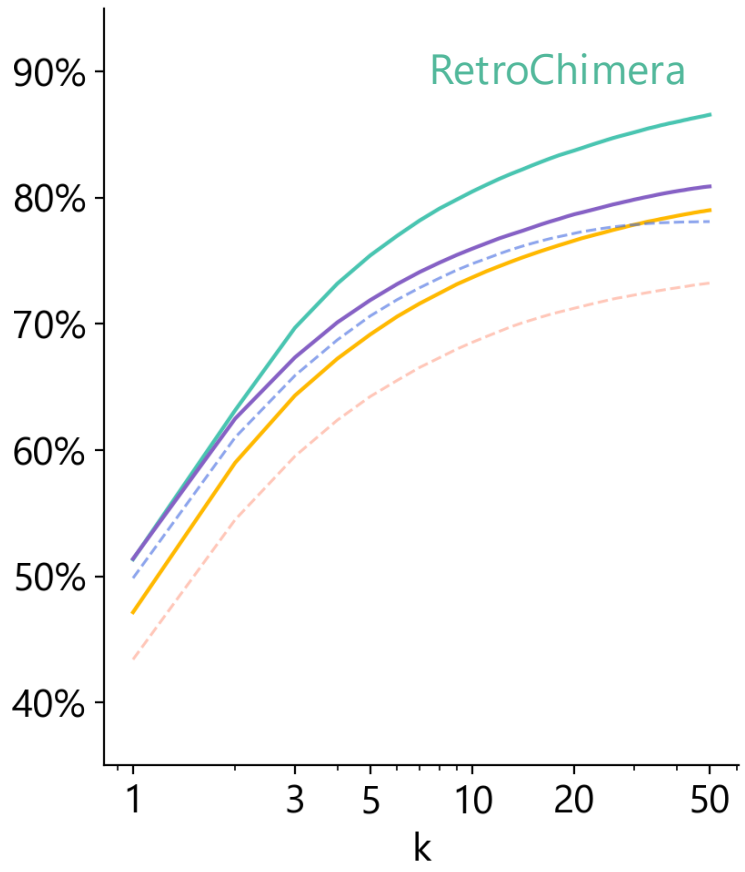
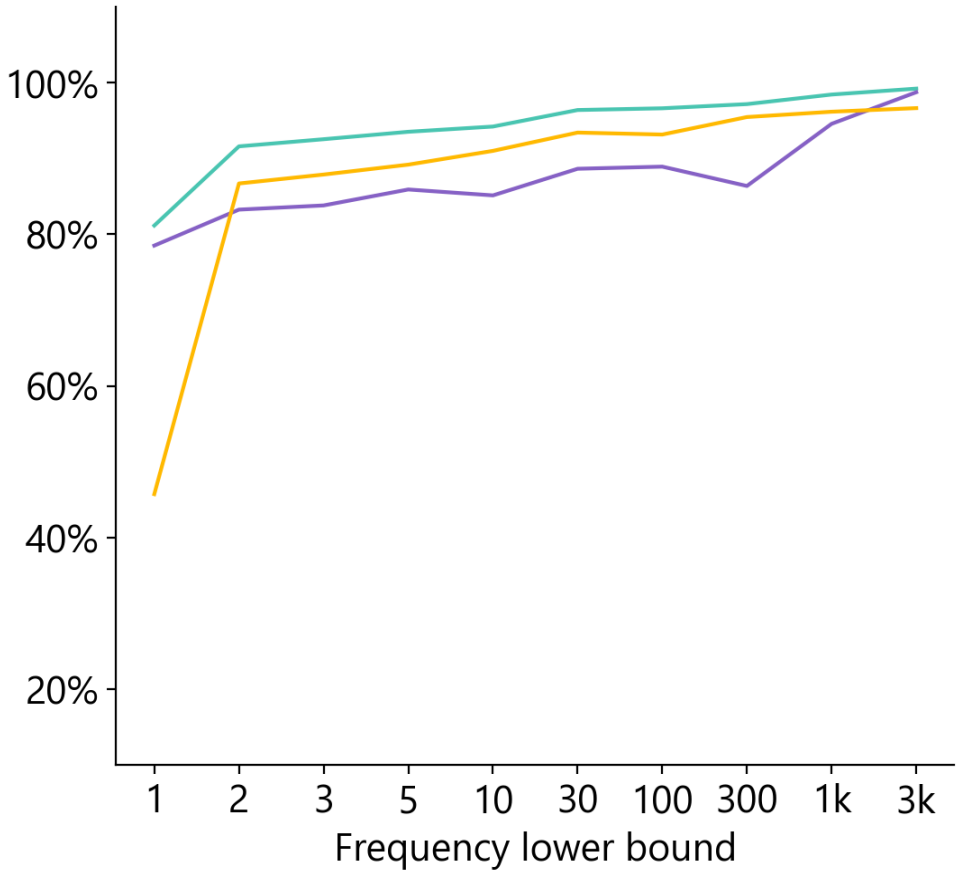
Top-k single-step prediction accuracy



Top-50 accuracy vs template support



Performance is robust OOD

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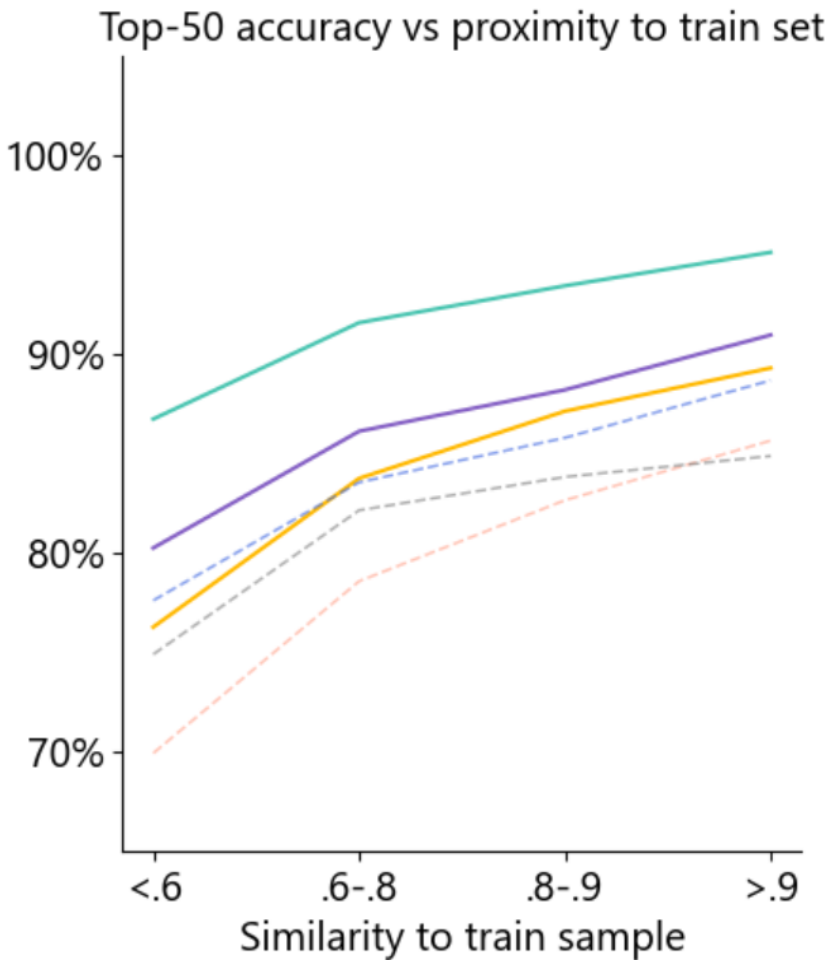

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How to combine individual reactions into full plans?

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Synthesis prediction models and search

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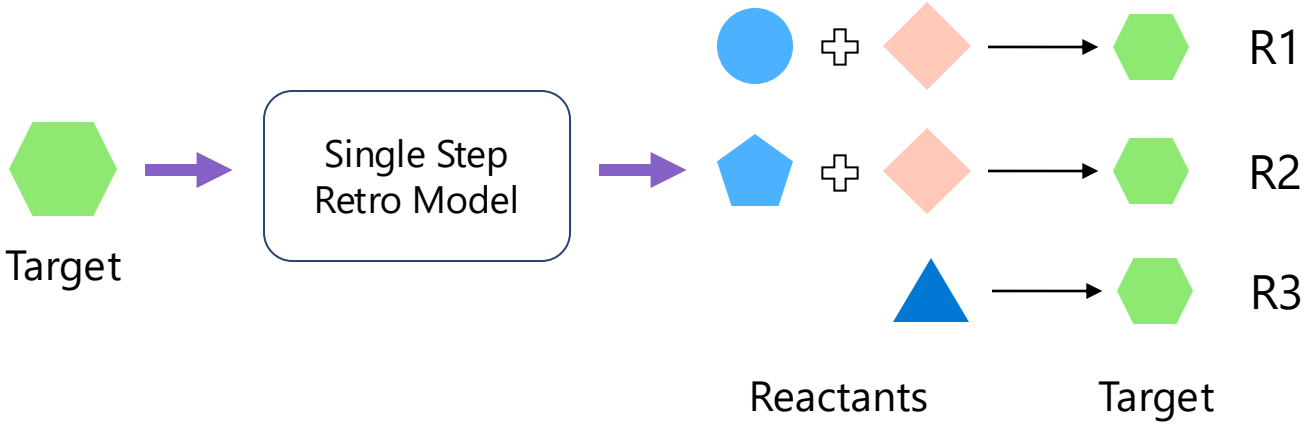
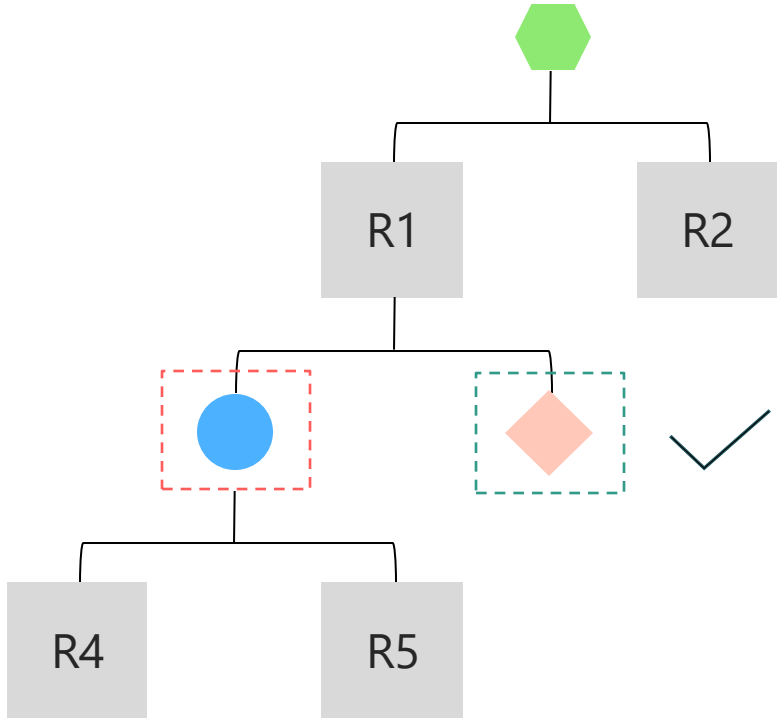
(1) Given target, predict different possible reactants



(2) Apply model recursively to obtain routes



(2) Maziarz et al, "Re-evaluating Retrosynthesis Algorithms with Syntheseus", Faraday Discuss. 2024
Liu et al, "Retrosynthetic Planning with Dual Value Networks", ICML 2023

Search with RetroChimera

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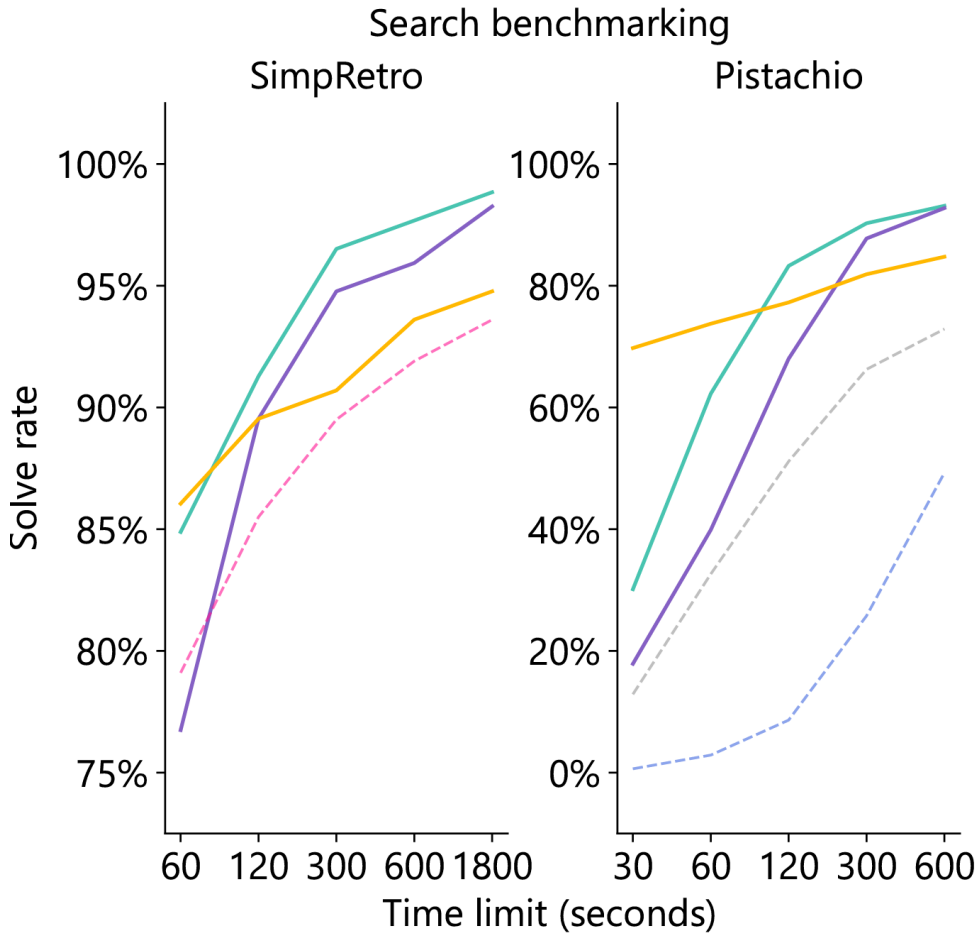

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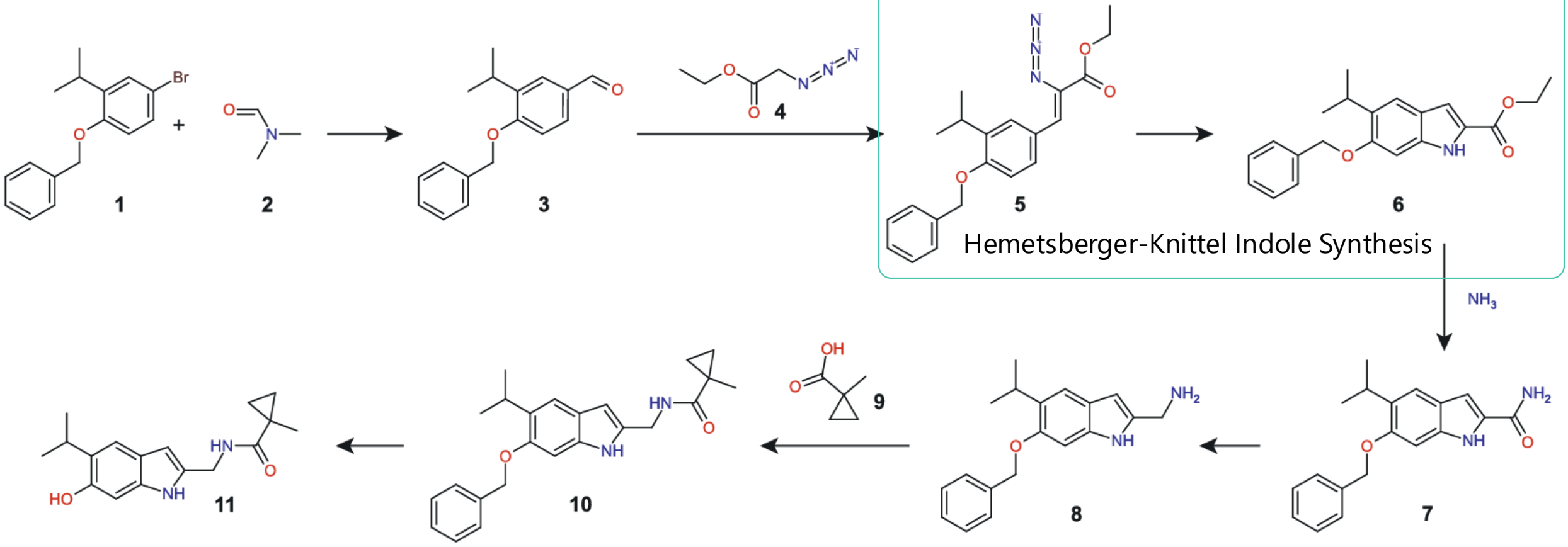
Example synthesis plan



RetroChimera can find non-trivial routes

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Exploring RetroChimera's predictions qualitatively

Microsoft Research

Denoising

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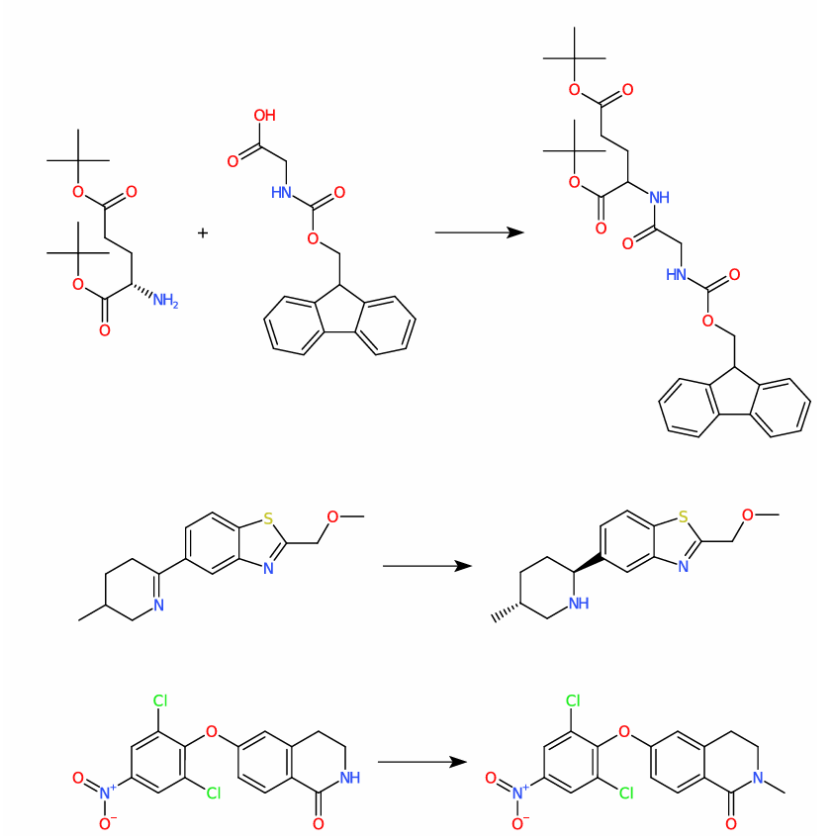
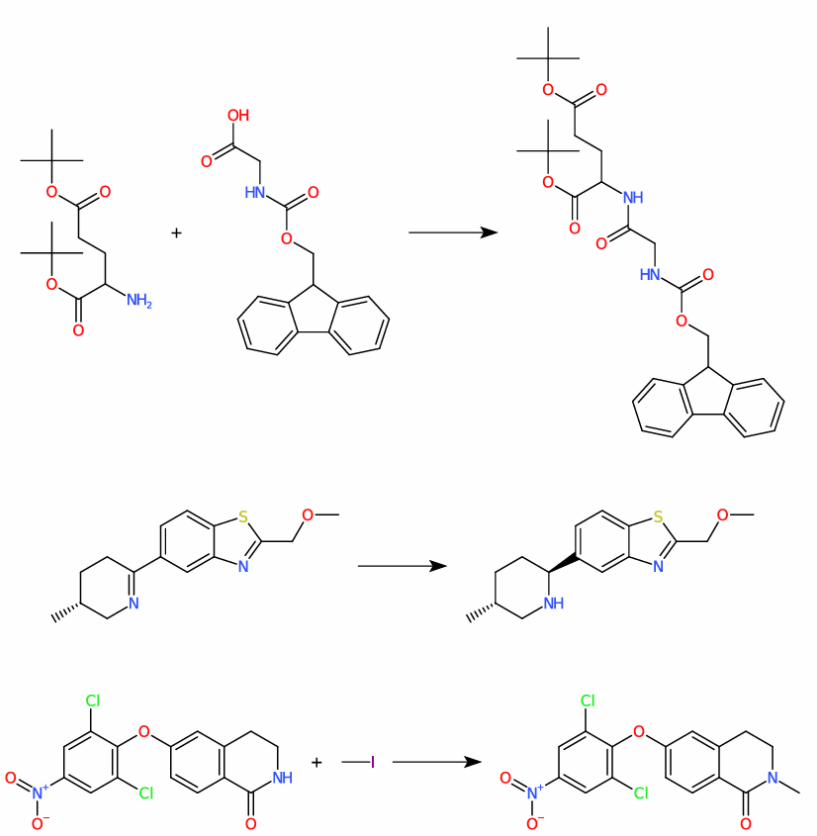


original patent reaction



denoised by RetroChimera

Pairwise (blind) expert comparisons

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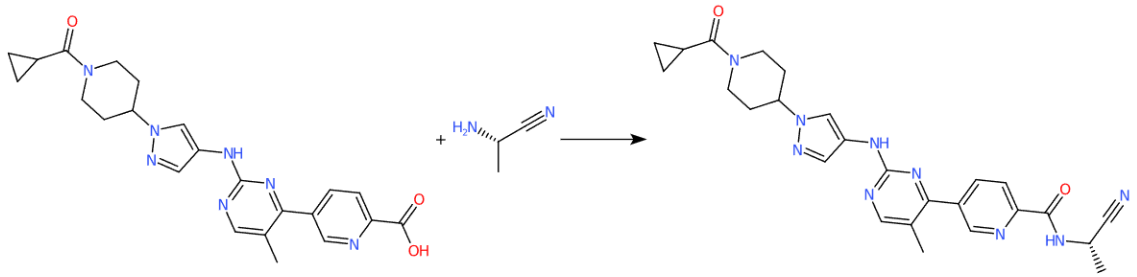
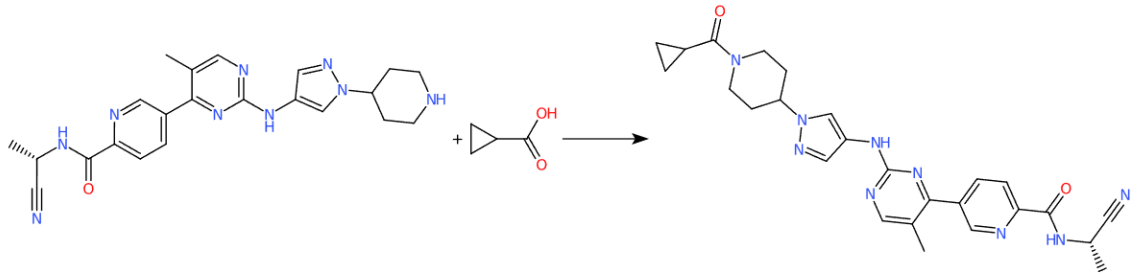
Please pick your preferred reaction.

Model 1:



Model 2:



Model 1 better

Model 2 better

Both good

Both bad

Sample ID: ed2e9b78-bed5-43a5-b399-928248f08c2f

Experiment ID: 12

Preferences in pairwise expert comparisons

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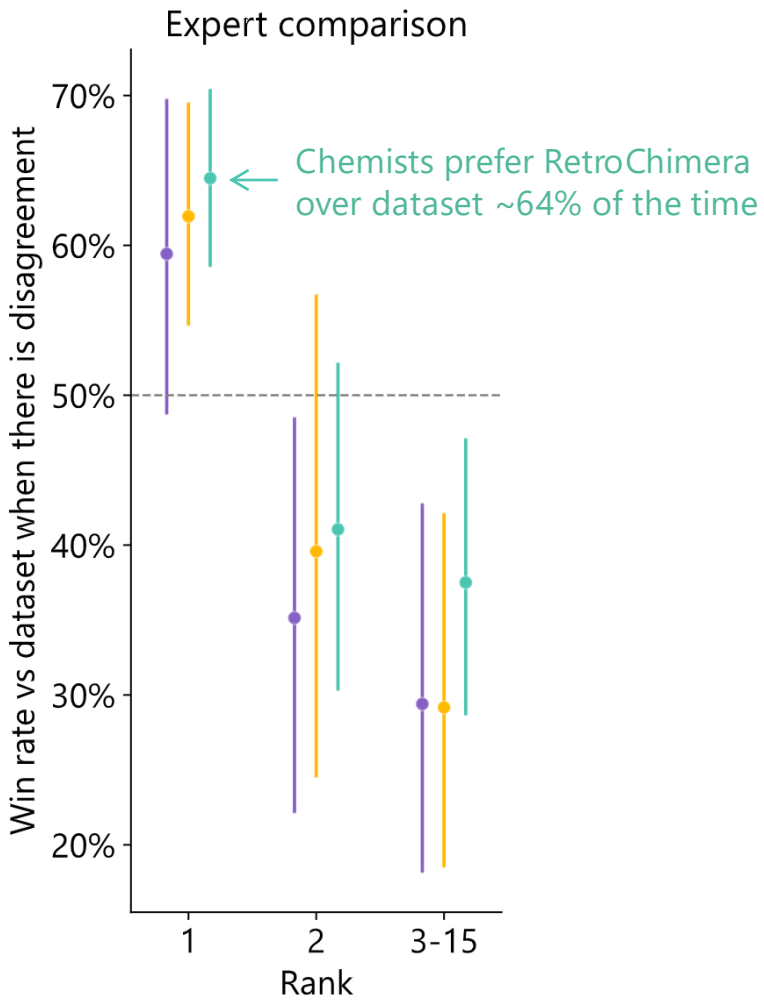
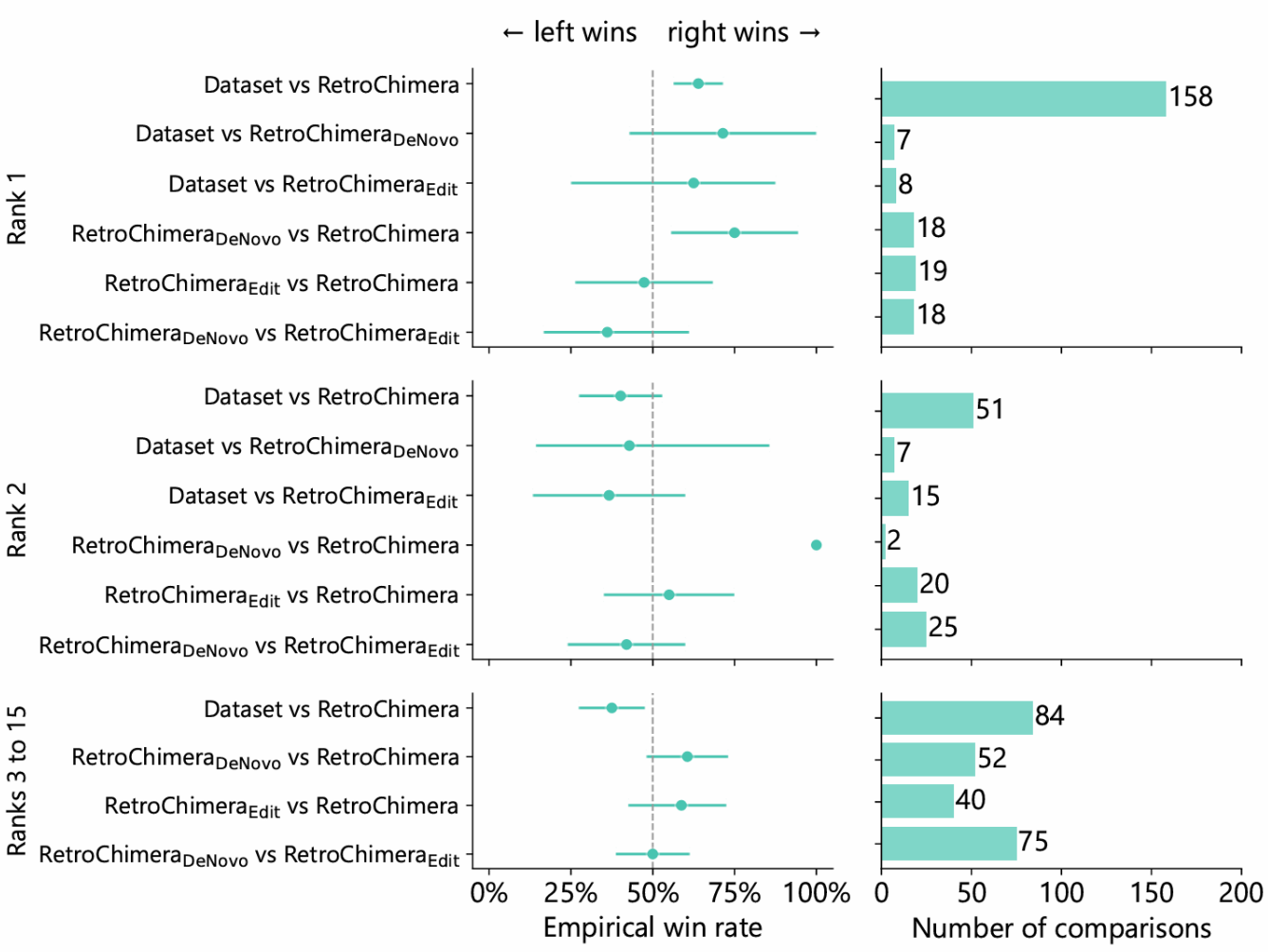
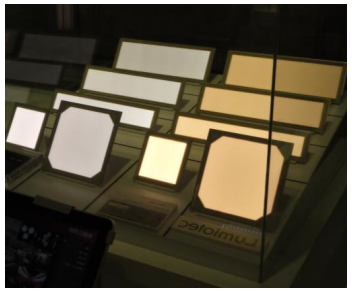




Questions

Our goal: Help chemists discover new essential molecules with predictive synthesis



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`aka.ms/RetroChimeraPaper`

`aka.ms/RetroChimeraCode` (github.com/microsoft/retrochimera)

`aka.ms/CondPredPaper` (cond. pred. model QFANG, coming soon)

`github.com/microsoft/syntheseus`