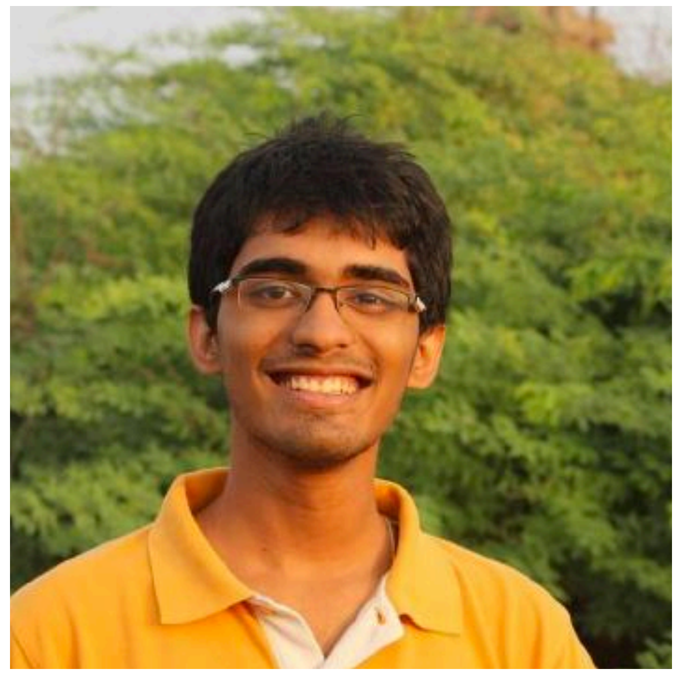
Learning Graph Models for Retrosynthesis Prediction



Vignesh Ram Somnath

Charlotte Bunne

Connor Coley

Andreas Krause

Regina Barzilay

MIT and ETH zürich

Outline

Problem Introduction

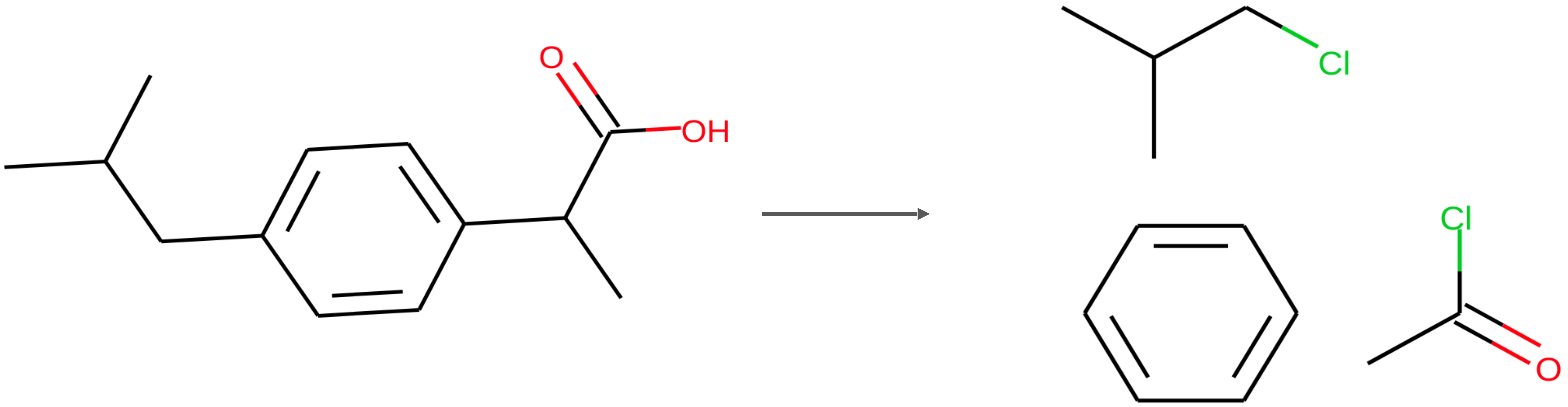
Prior Work

Model Formulation

Experiments and Conclusion

Retrosynthesis

Given a target molecule, predict precursors that can be used to design it

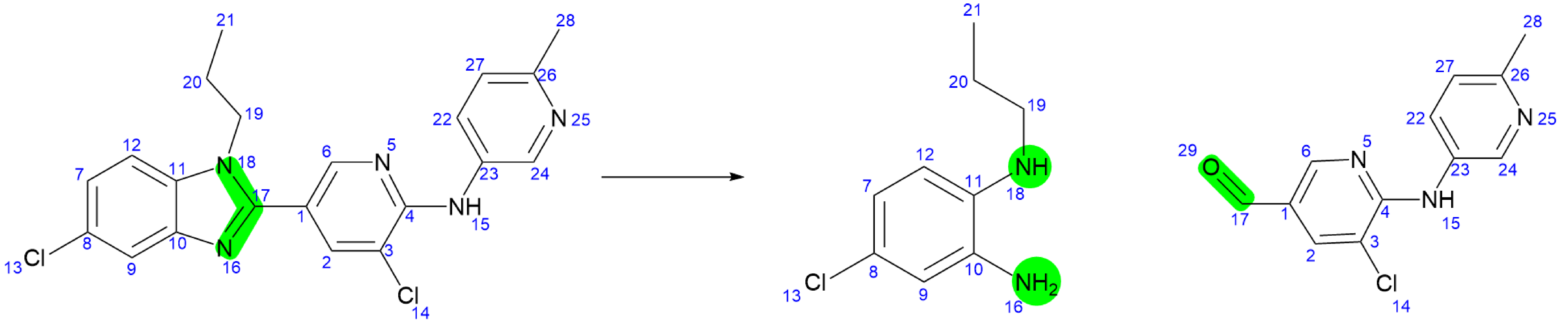


Ibuprofen

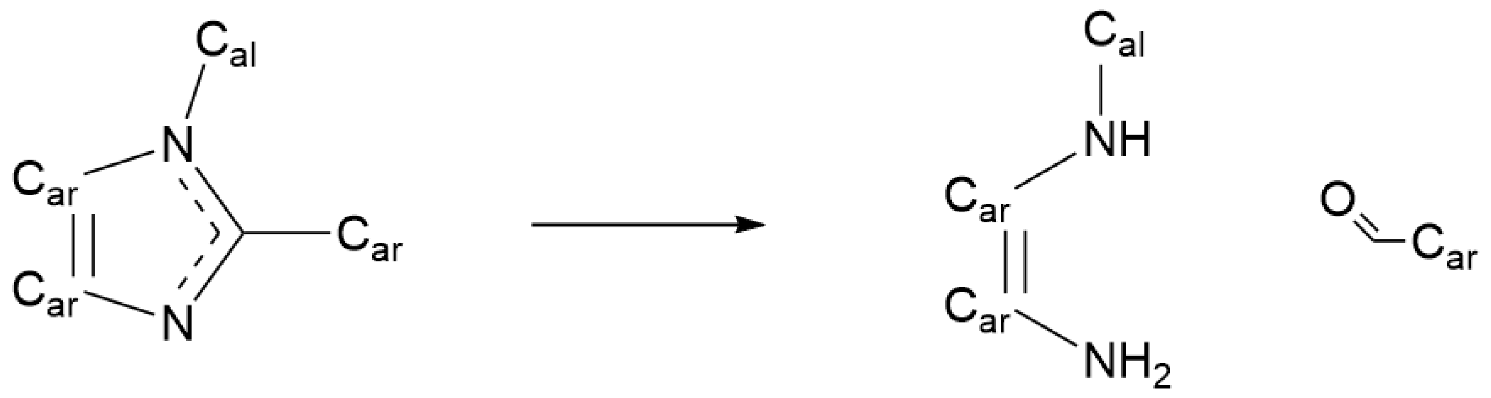
Ibuprofen precursors

Prior Work: Template-Based

Example Reaction



Corresponding Template



C$_{ar}$ = Aromatic carbon
C$_{al}$ = Aliphatic carbon

Coley et al. (2017), Segler et al. (2017), Dai et al. (2019)

Prior Work: Template-Based

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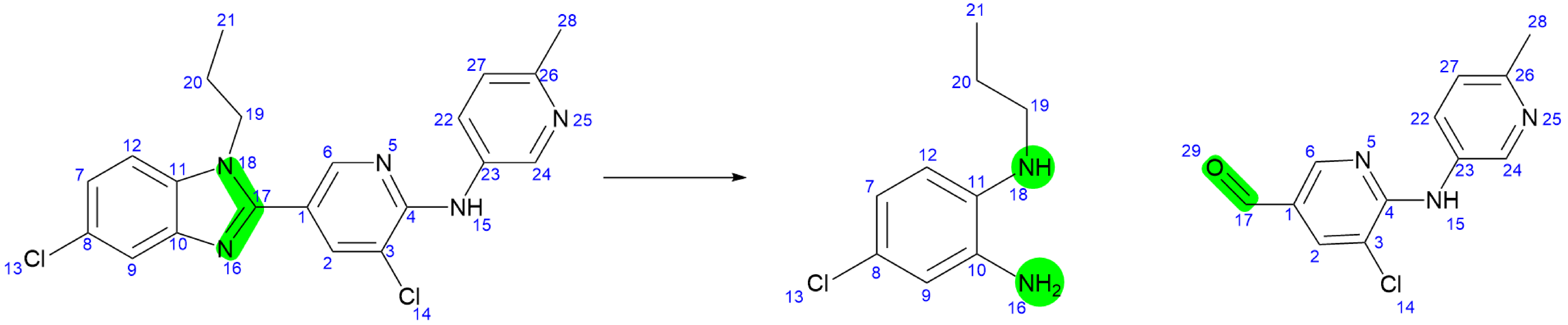

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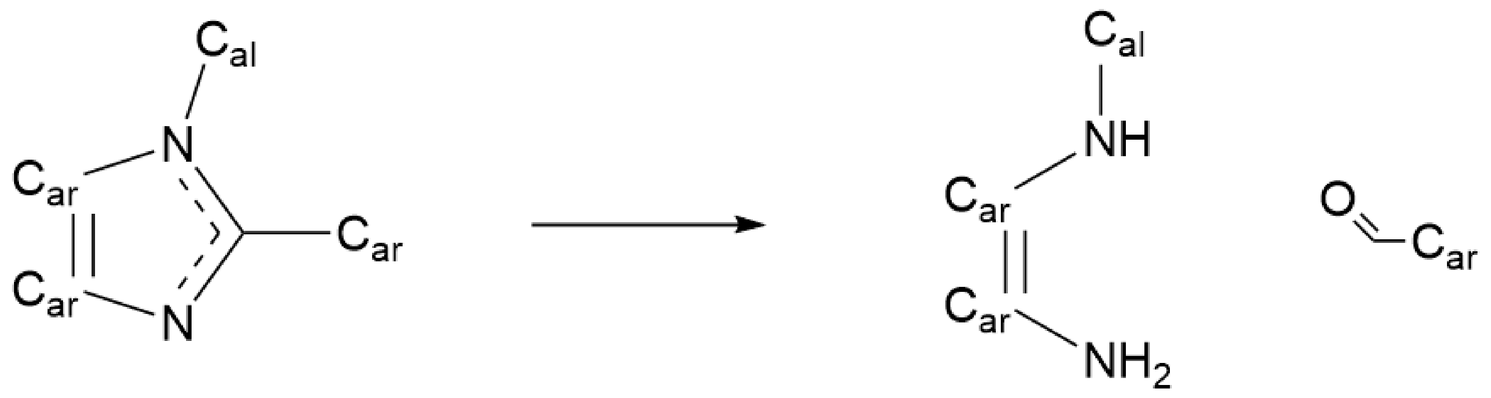

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- Relevance: Rules for a given molecule

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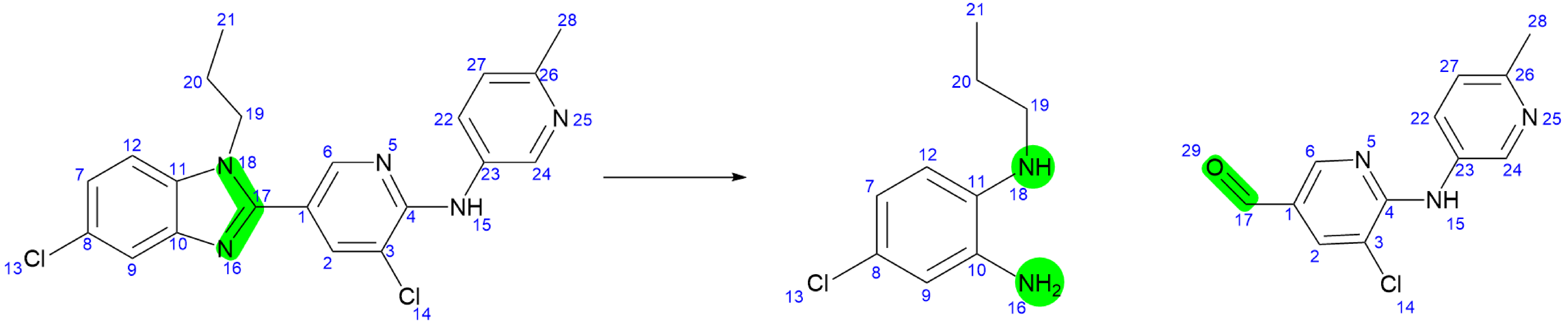

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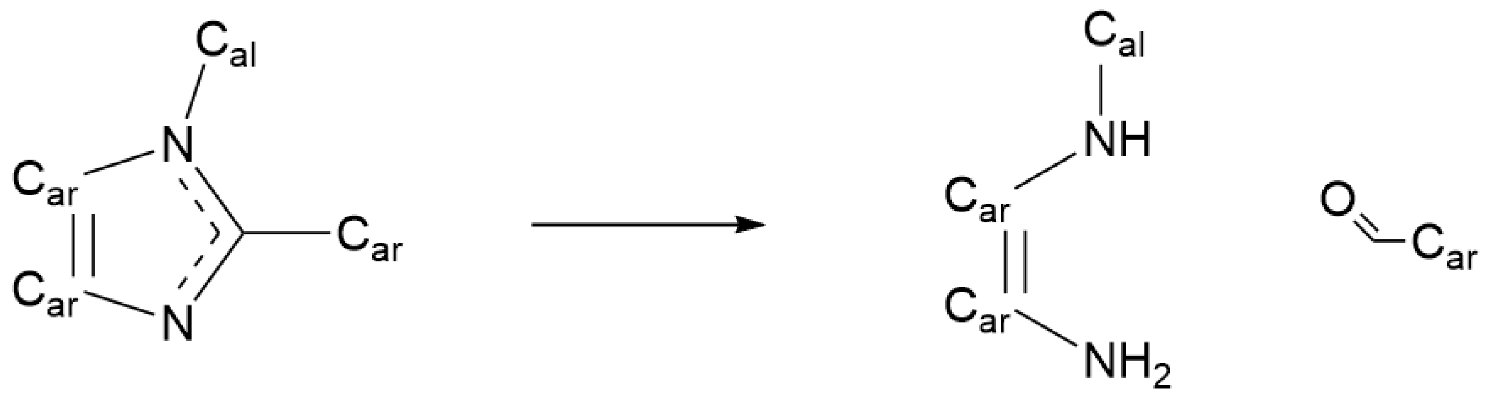

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Advantages:

- Interpretable - Knowledge of template (and reaction type)

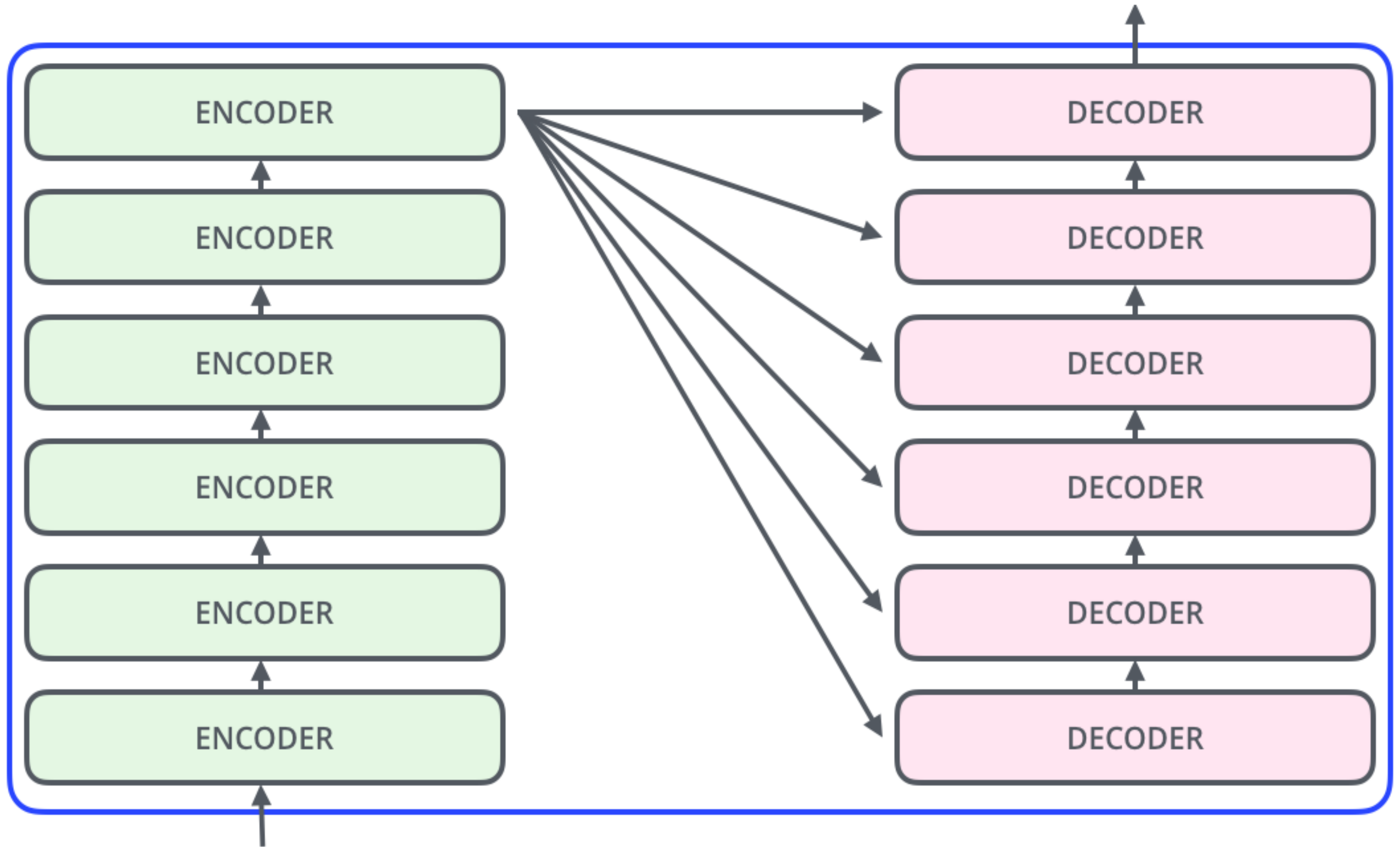
Disadvantages:

- Incomplete coverage of test set
- Cannot generalize outside rule set

- Coverage vs scalability tradeoff
- Relevance: Rules for a given molecule

Prior Work: Template-Free

Cc1cccc(C#C[Si](C)(C)C)n1.Cn1nccc1-c1ccc(Br)cc1



Cc1cccc(C#Cc2ccc(-c3ccnn3C)cc2)n1

Schwaller et al. (2019)
Zheng et al. (2019)
Chen et al. (2020)

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Figure: http://jalammar.github.io/illustrated-transformer/

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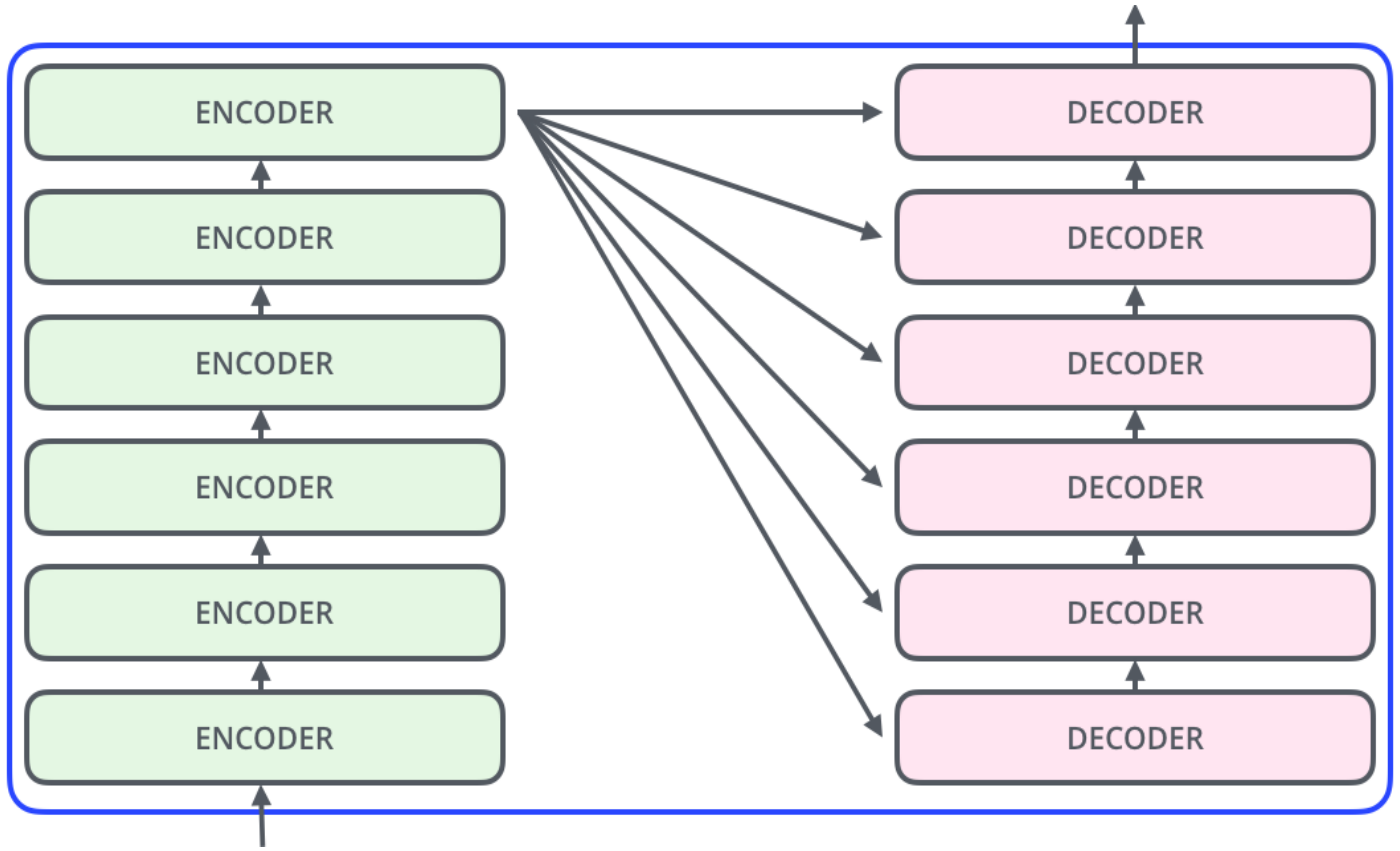

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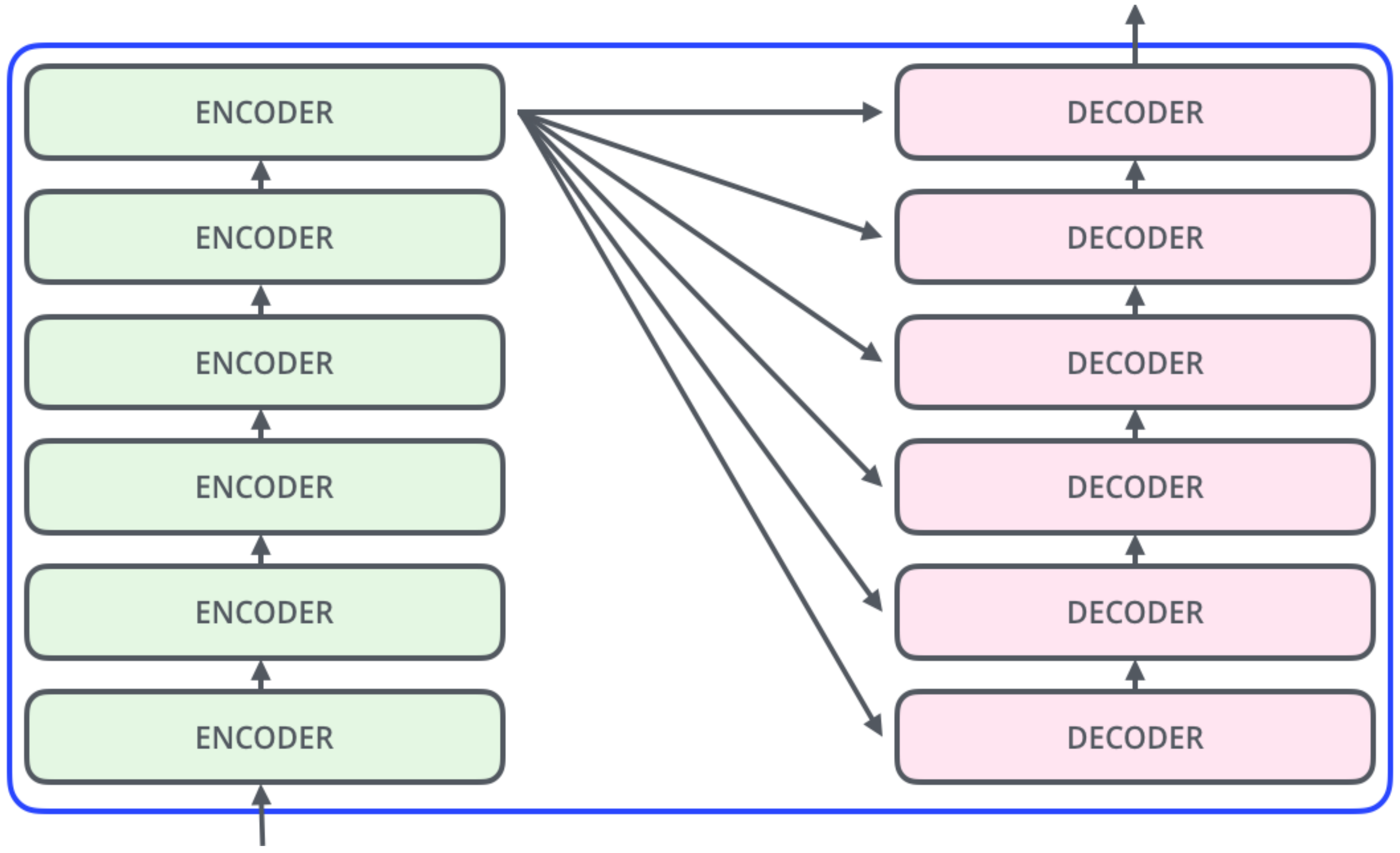

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Advantages:

- Flexibility in learning transformations

Disadvantages:

- Poor interpretability
- Fails to utilize conserved substructures

- Discover reaction rules automatically

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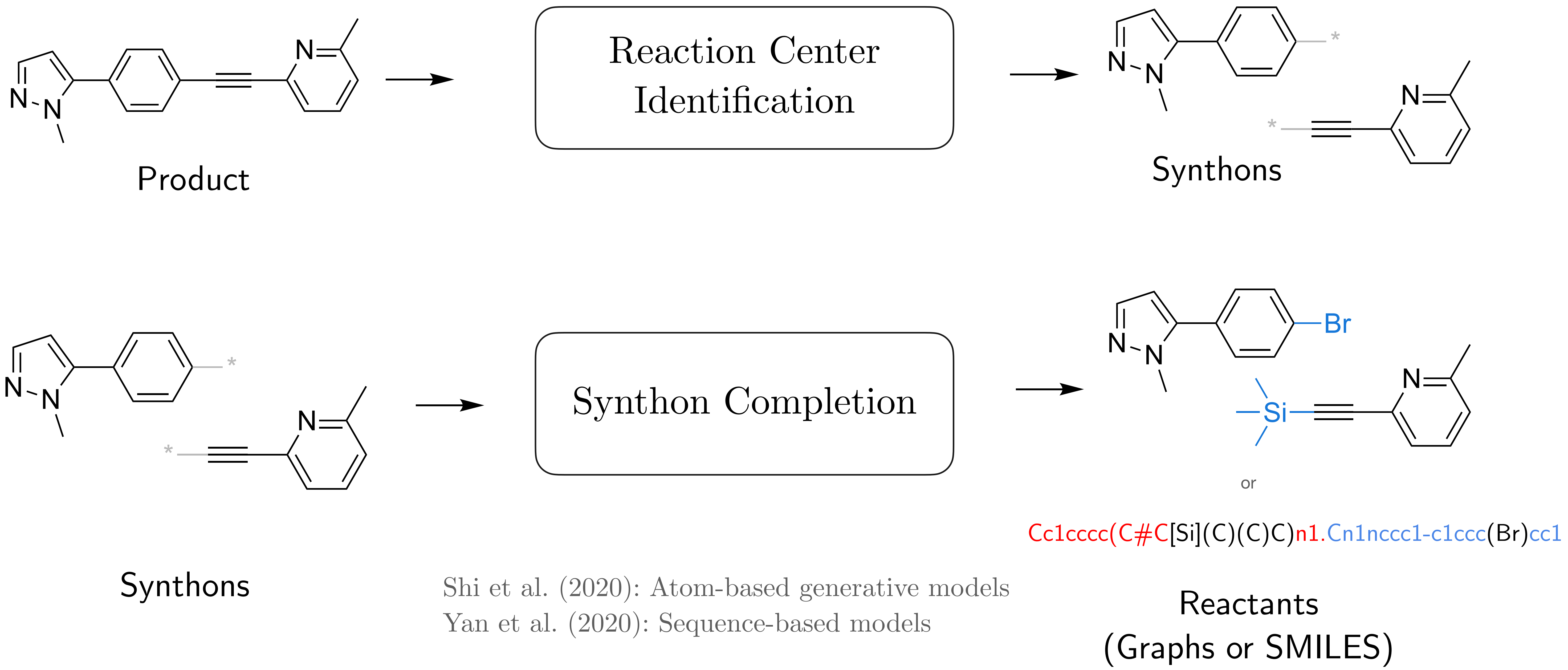
Prior Work: Semi-Template-Based



Product → Reaction Center Identification → Synthons

Synthons → Synthon Completion → Reactants (Graphs or SMILES)

or

Cc1cccc(C#C[Si](C)(C)C)n1.Cn1nccc1-c1ccc(Br)cc1

Shi et al. (2020): Atom-based generative models
Yan et al. (2020): Sequence-based models

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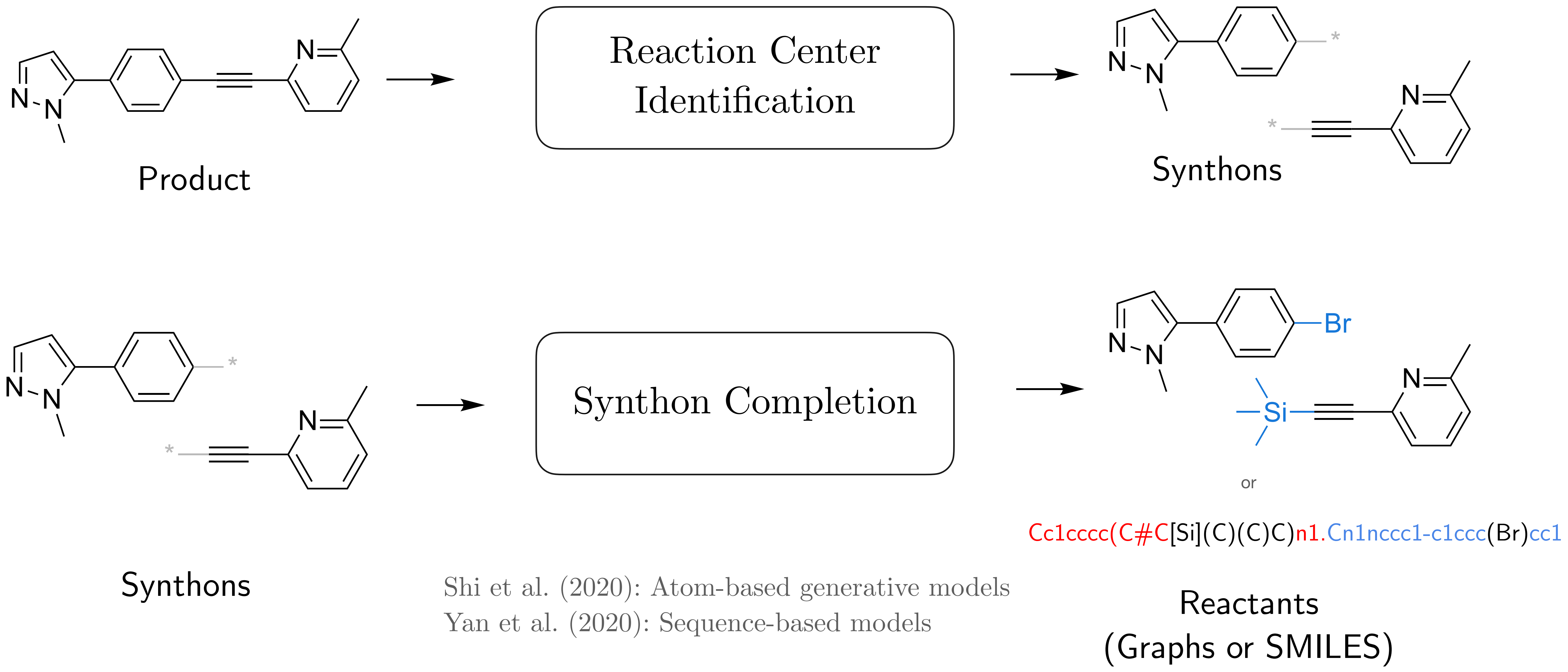

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Shi et al. (2020): Atom-based generative models
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Advantages:

1. Closer to a chemist's intuition
2. Improved interpretability

Disadvantages:

1. Fails to utilize conserved substructures in synthon completion

Motivation

Build a retrosynthesis model to identify and utilize conserved substructures

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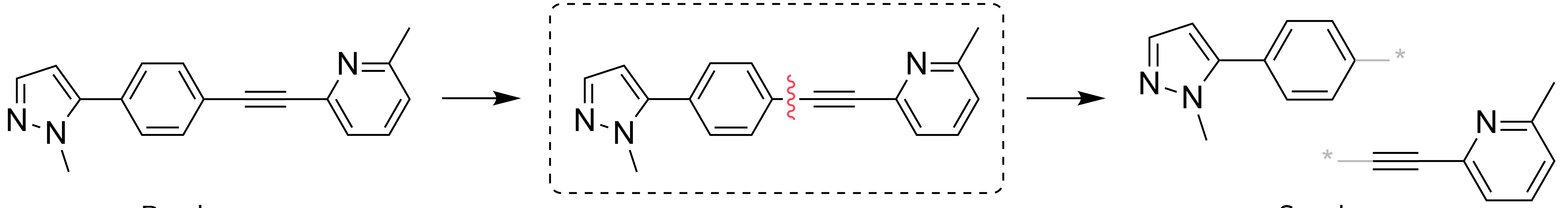
Advantages

- *Interpretability* - Captures a chemists workflow about retrosynthesis
- *Efficiency* - More efficient use of the data, by not generating/completing molecules from scratch
- *Generalization* - Stronger inductive biases, fewer invalid suggestions

Proposed Formulation

Edit Prediction



Product

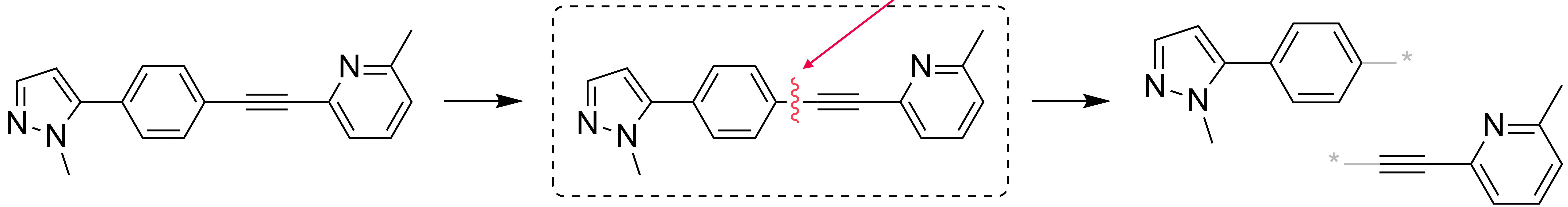
Synthons

Proposed Formulation

Bond Edit

change in bond order

Edit Prediction



Product

Synthons

Synthons

disconnected components after applying the edit

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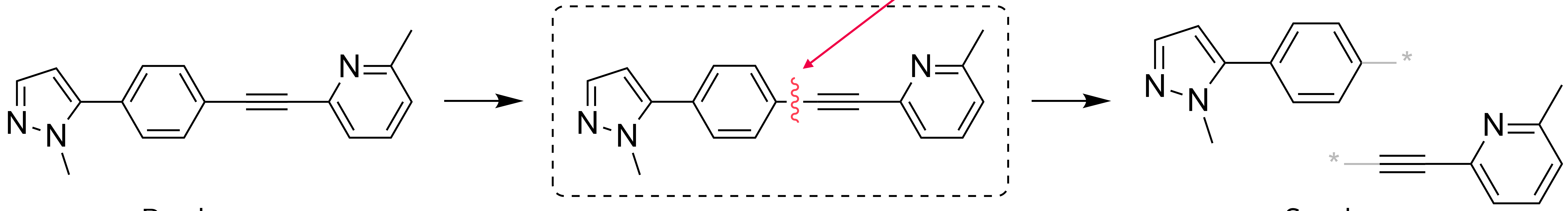

Product

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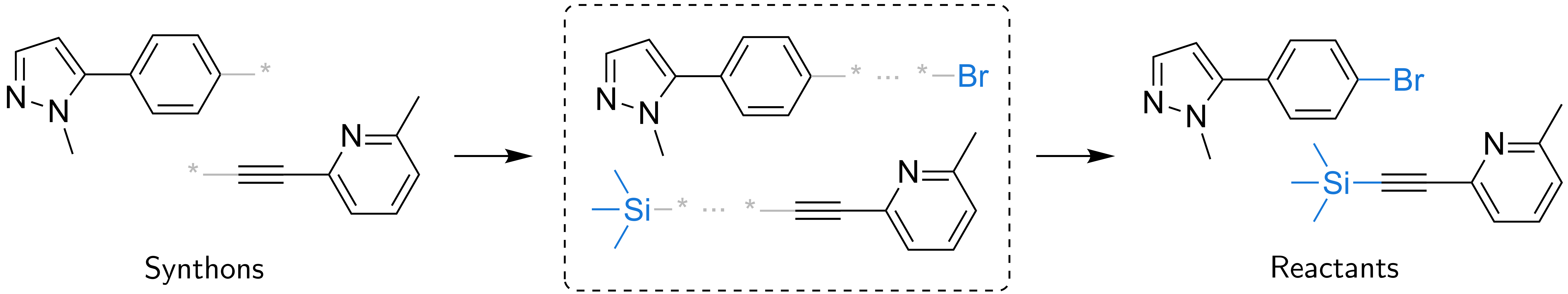
Synthon Completion



Synthons

Reactants

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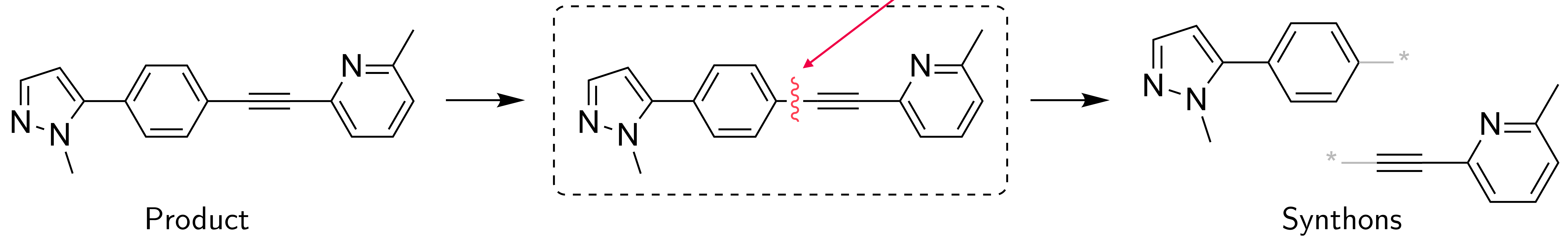

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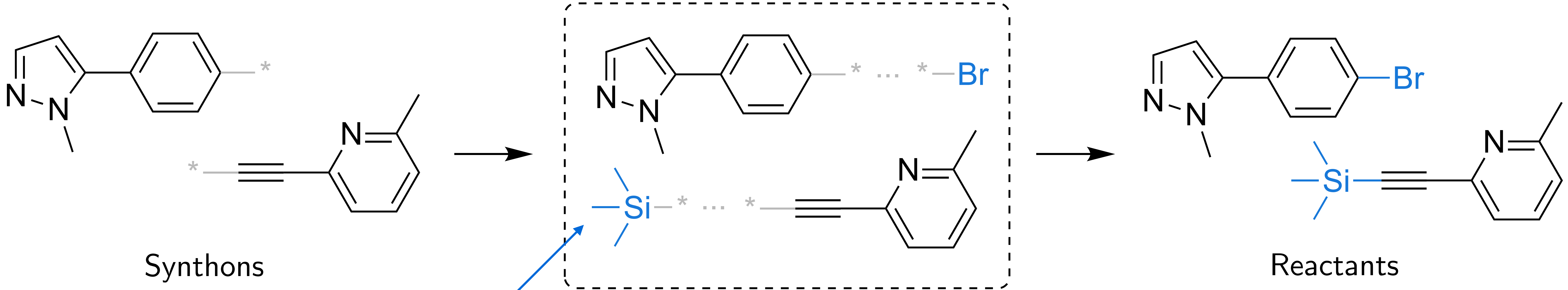
Synthon Completion



Leaving Groups
subgraphs added to synthons to produce reactants

and

Edit Prediction

Extracting Edits

Compare atom-maps of products and reactants to identify atoms/bonds undergoing a change

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Initial Prediction Task

- Use atom and bond representations to predict scores for possible edits
- Allowed edits:
  Whether the hydrogen atom count for a given atom changes (0 or 1)
  Change in the bond type of a given bond (5 possible values)

Edit Prediction

Extracting Edits

Compare atom-maps of products and reactants to identify atoms/bonds undergoing a change

Initial Prediction Task

- Use atom and bond representations to predict scores for possible edits
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Edit Correction

- Leverage dependencies between edits to update initial edit scores
  e.g. aromatic rings are stable and tend to remain unchanged
- LSTM style update on line-graph based representations

Train with cross-entropy loss over possible edits in the molecule

Synthon Completion

Leaving Group Vocabulary Extraction

- Extract subgraphs based on atom-maps only present in reactants
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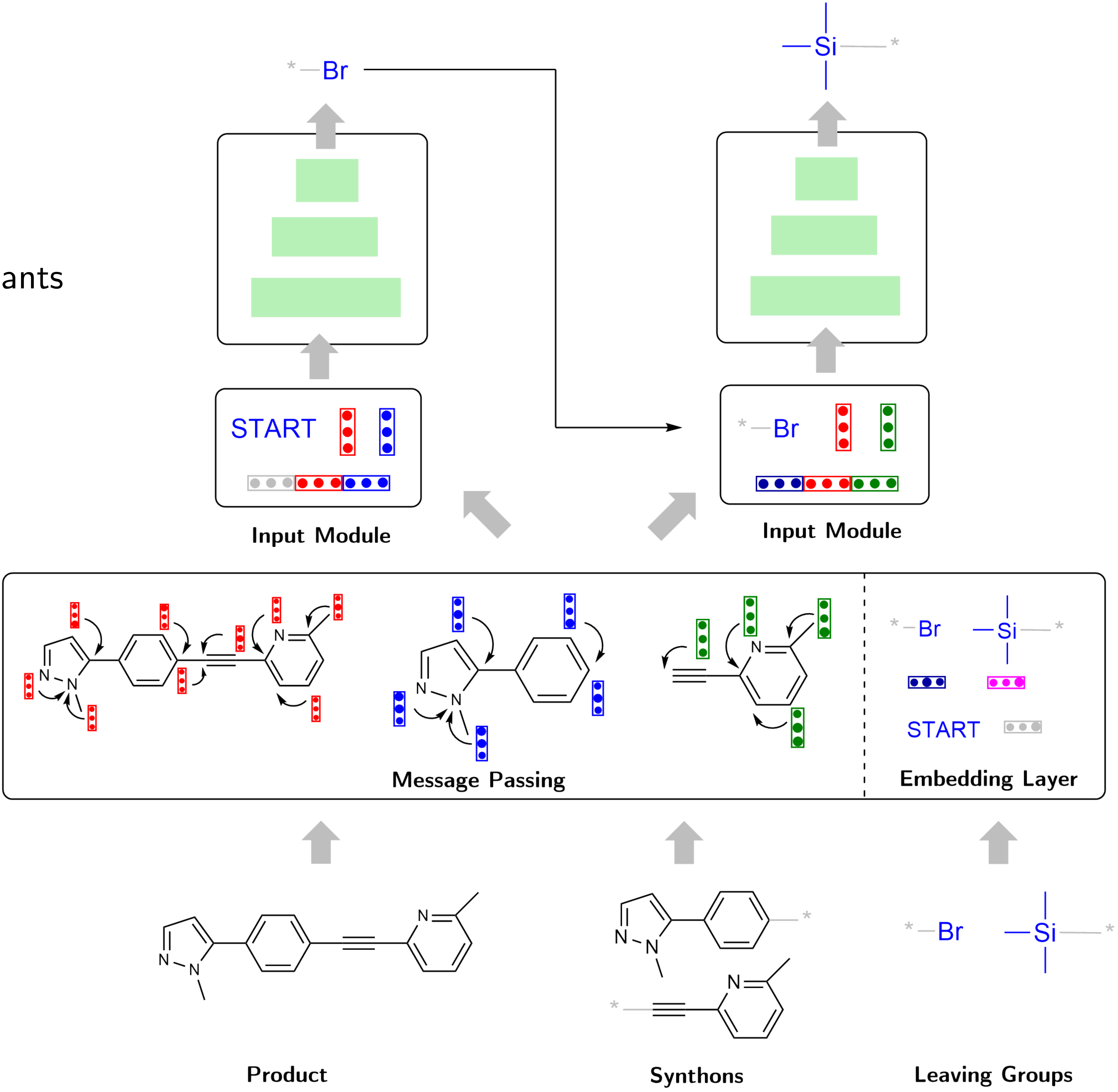

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Experimental Setup

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Dataset

- USPTO-50k - Standard benchmark dataset
- 50K reactions across 10 reaction classes
- Training/validation/test in a 8:1:1 split (40K train, 5K valid, 5K test)

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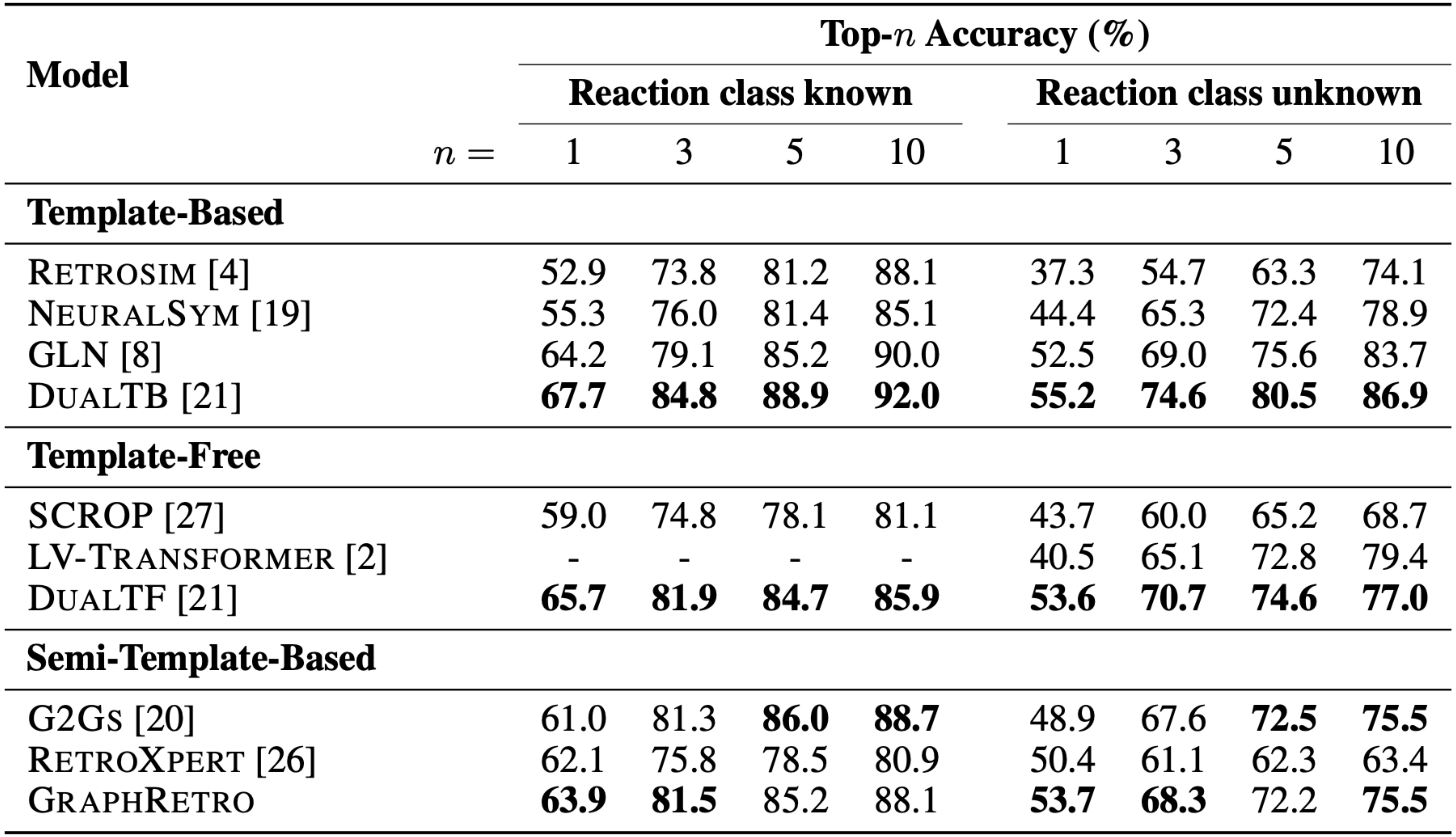
Evaluation

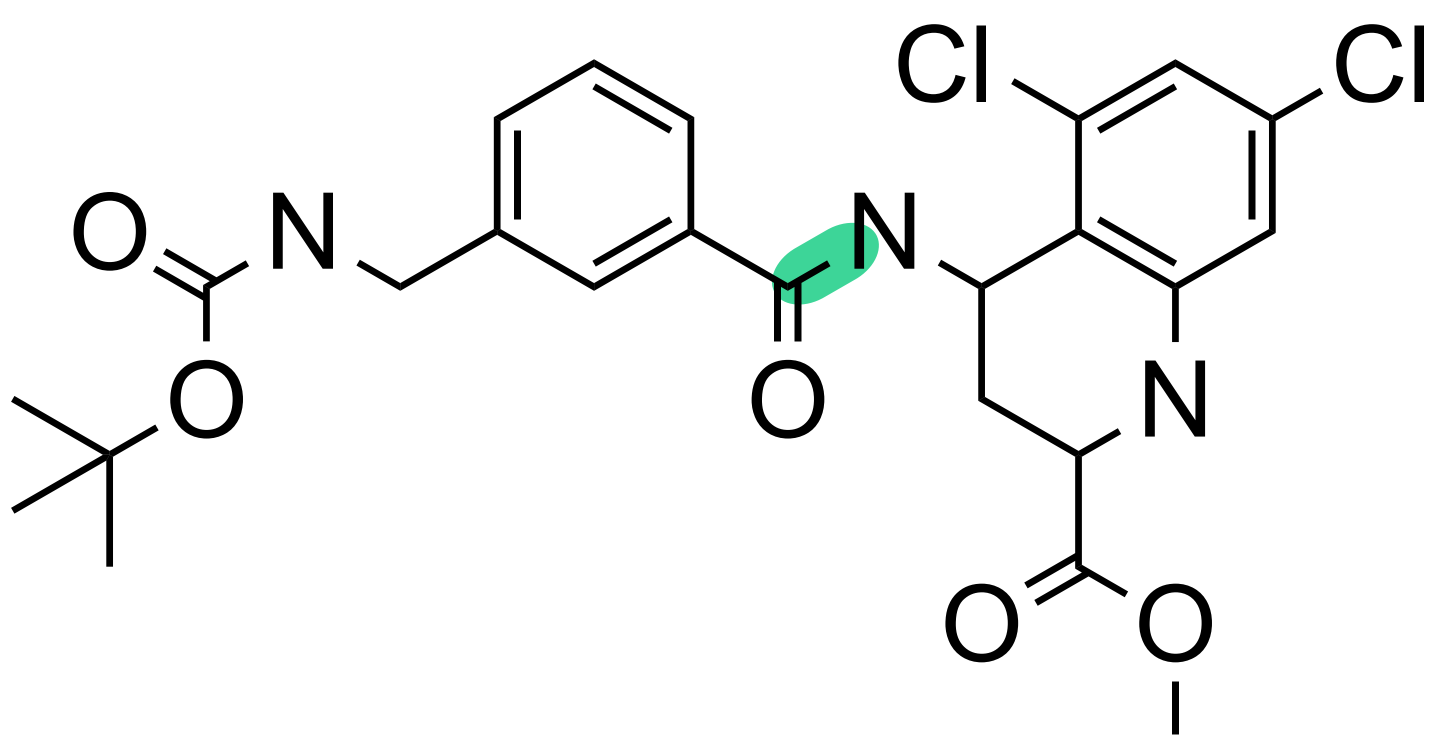
- Top-n accuracy ($n = 1, 3, 5, 10$)
- Compare canonical SMILES of generated reactants to ground truth
- Reaction class known vs unknown

Retrosynthesis Performance

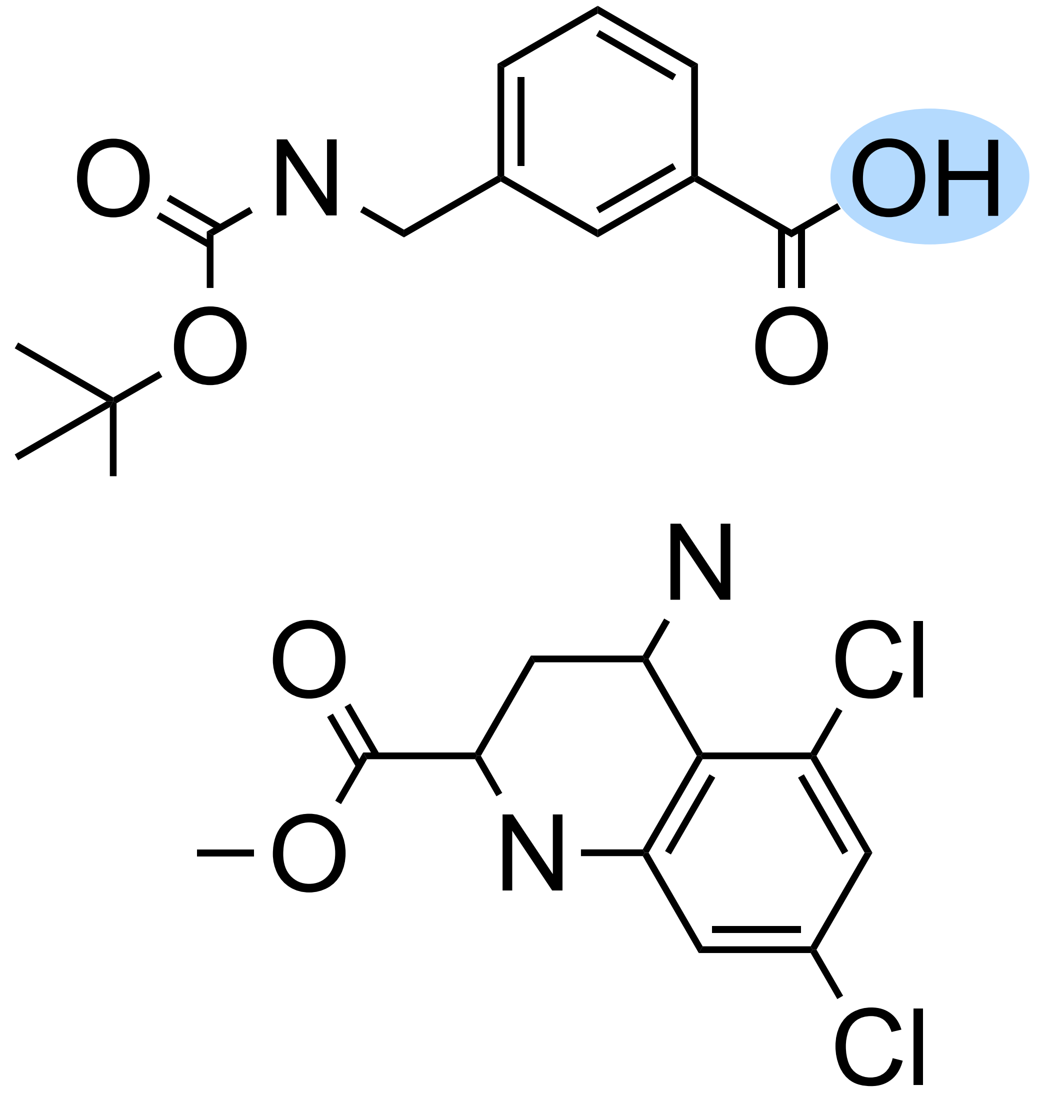


Model		Top-n Accuracy (%)							
		Reaction class known				Reaction class unknown			
	$n =$	1	3	5	10	1	3	5	10
Template-Based									
RetroSim [4]		52.9	73.8	81.2	88.1	37.3	54.7	63.3	74.1
NeuralSym [19]		55.3	76.0	81.4	85.1	44.4	65.3	72.4	78.9
GLN [8]		64.2	79.1	85.2	90.0	52.5	69.0	75.6	83.7
DualTB [21]		**67.7**	**84.8**	**88.9**	**92.0**	**55.2**	**74.6**	**80.5**	**86.9**
Template-Free									
SCROP [27]		59.0	74.8	78.1	81.1	43.7	60.0	65.2	68.7
LV-Transformer [2]		-	-	-	-	40.5	65.1	72.8	79.4
DualTF [21]		**65.7**	**81.9**	**84.7**	**85.9**	**53.6**	**70.7**	**74.6**	**77.0**
Semi-Template-Based									
G2Gs [20]		61.0	81.3	**86.0**	**88.7**	48.9	67.6	**72.5**	**75.5**
RetroXpert [26]		62.1	75.8	78.5	80.9	50.4	61.1	62.3	63.4
GraphRetro		**63.9**	**81.5**	85.2	88.1	**53.7**	**68.3**	72.2	**75.5**

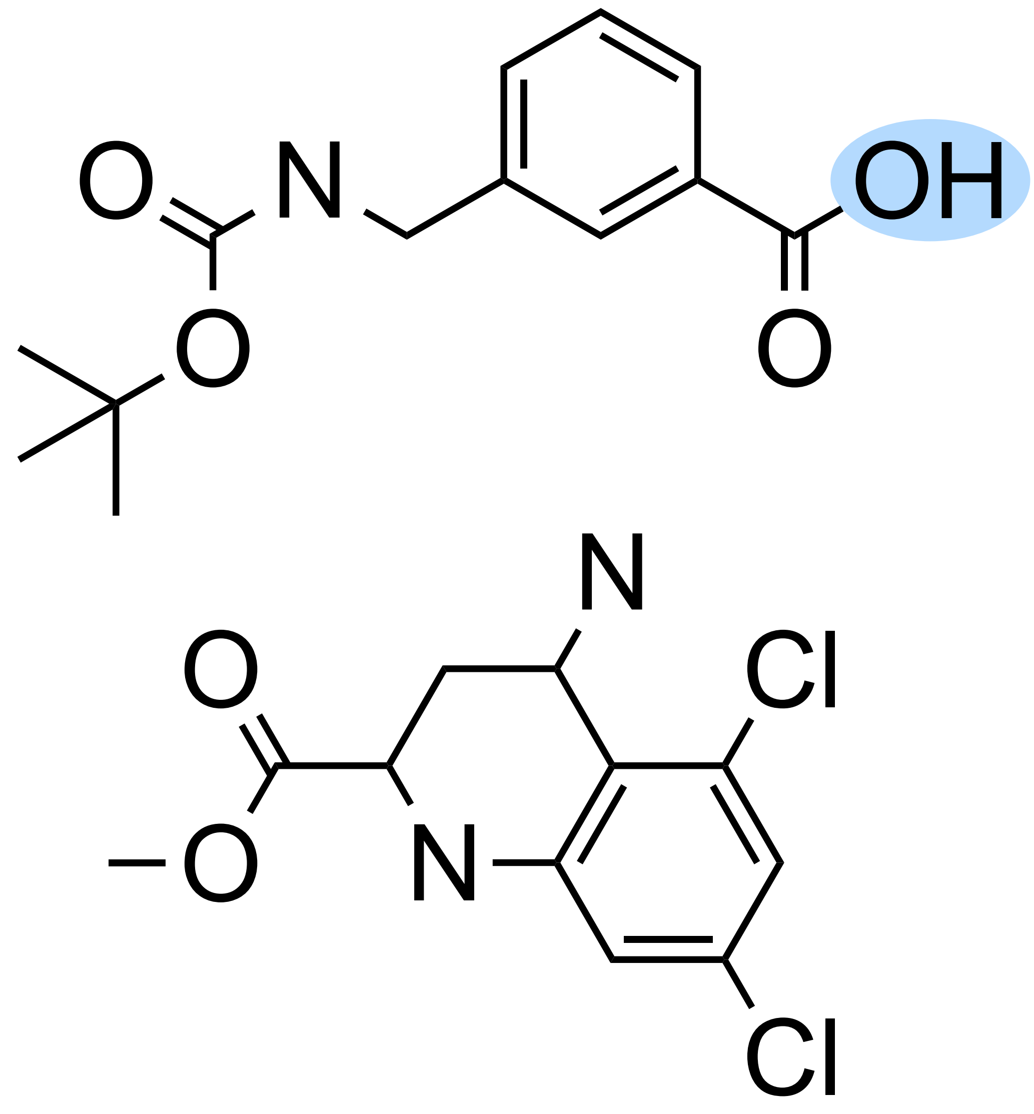
Example Predictions - Correct



Product



True Reactants

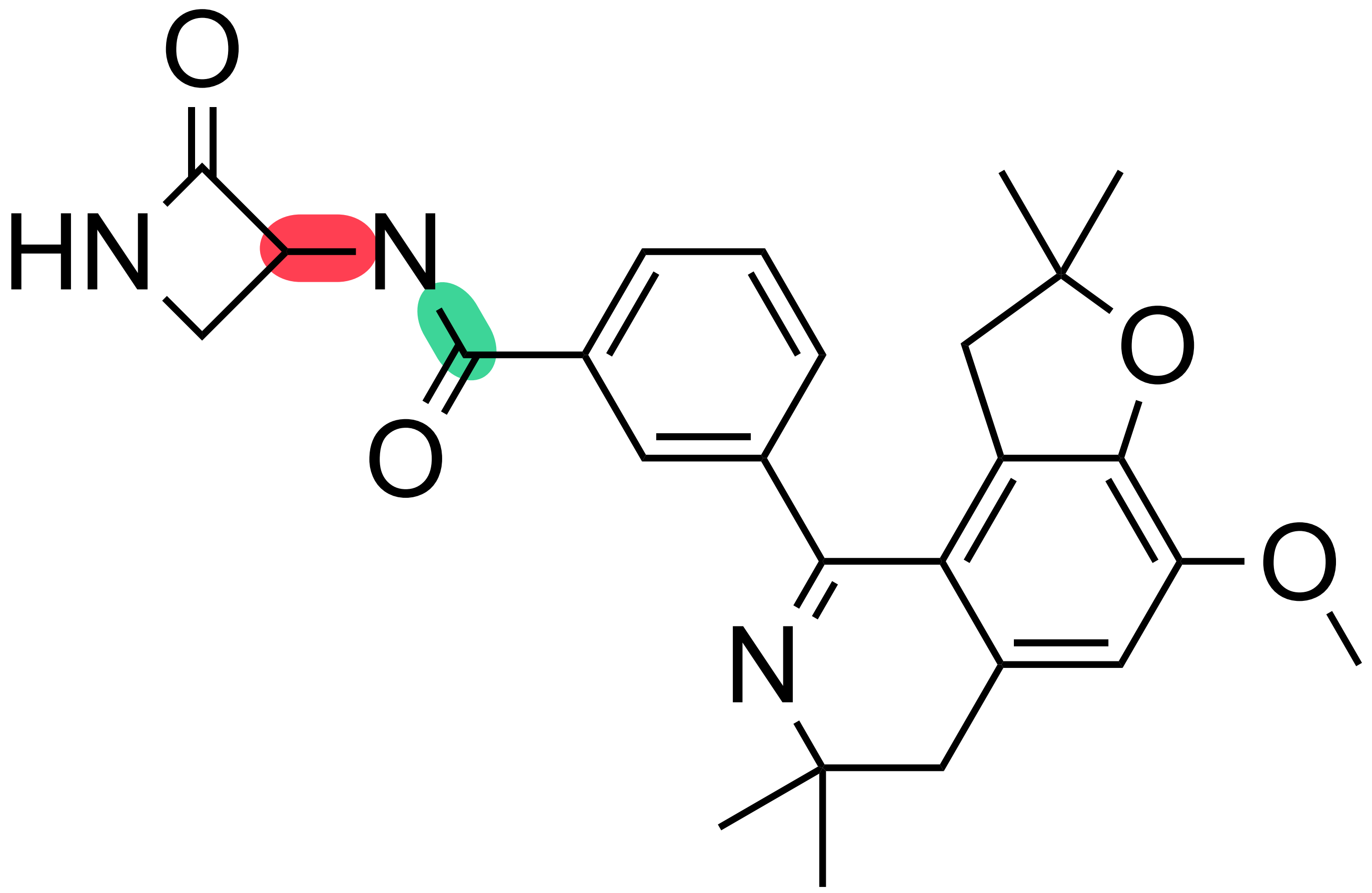


Predicted Reactants

🔵 leaving group 🟢 correct edit

Example Predictions - Incorrect

Incorrect edit, leaving groups predicted can't salvage the prediction



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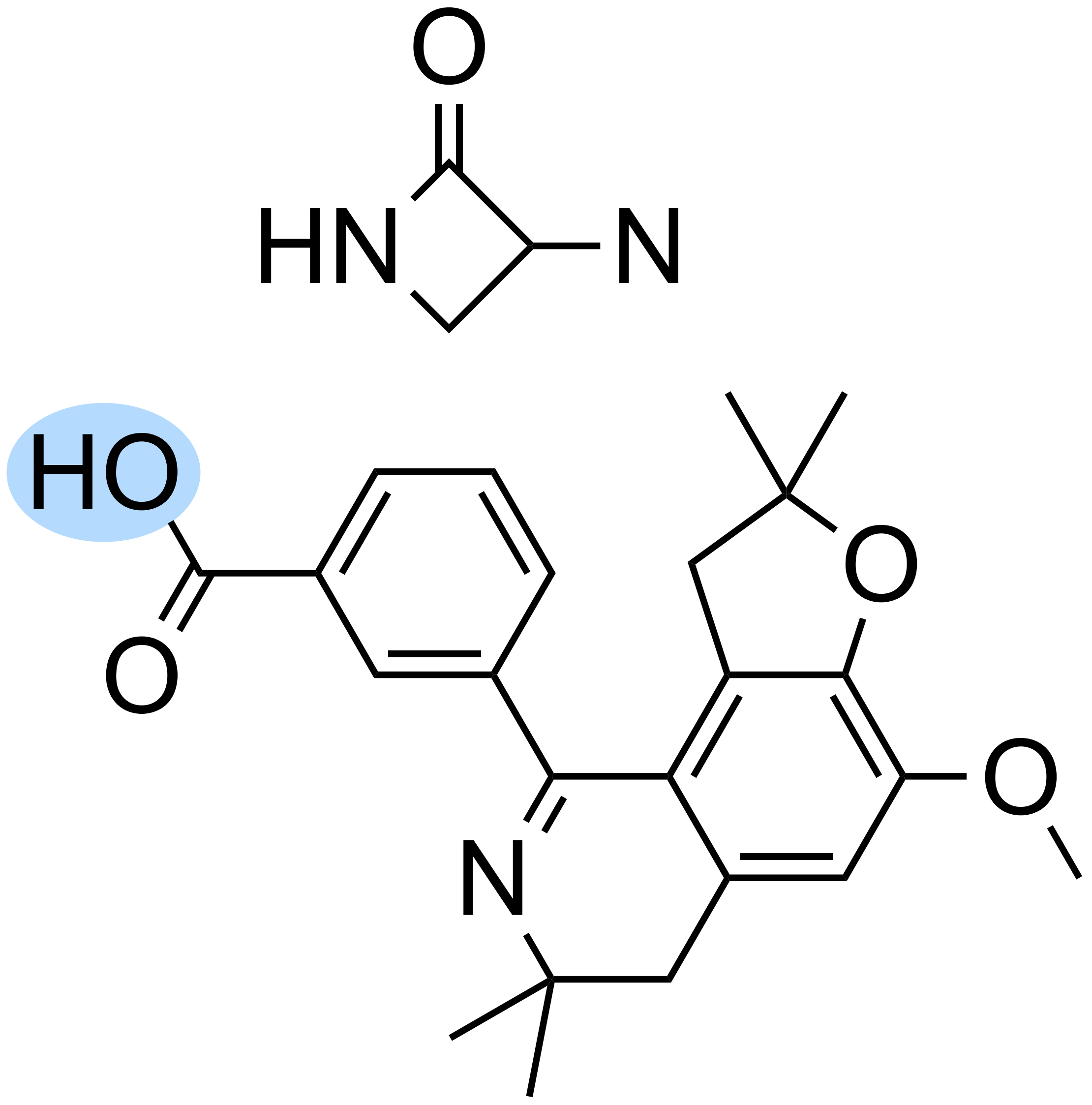

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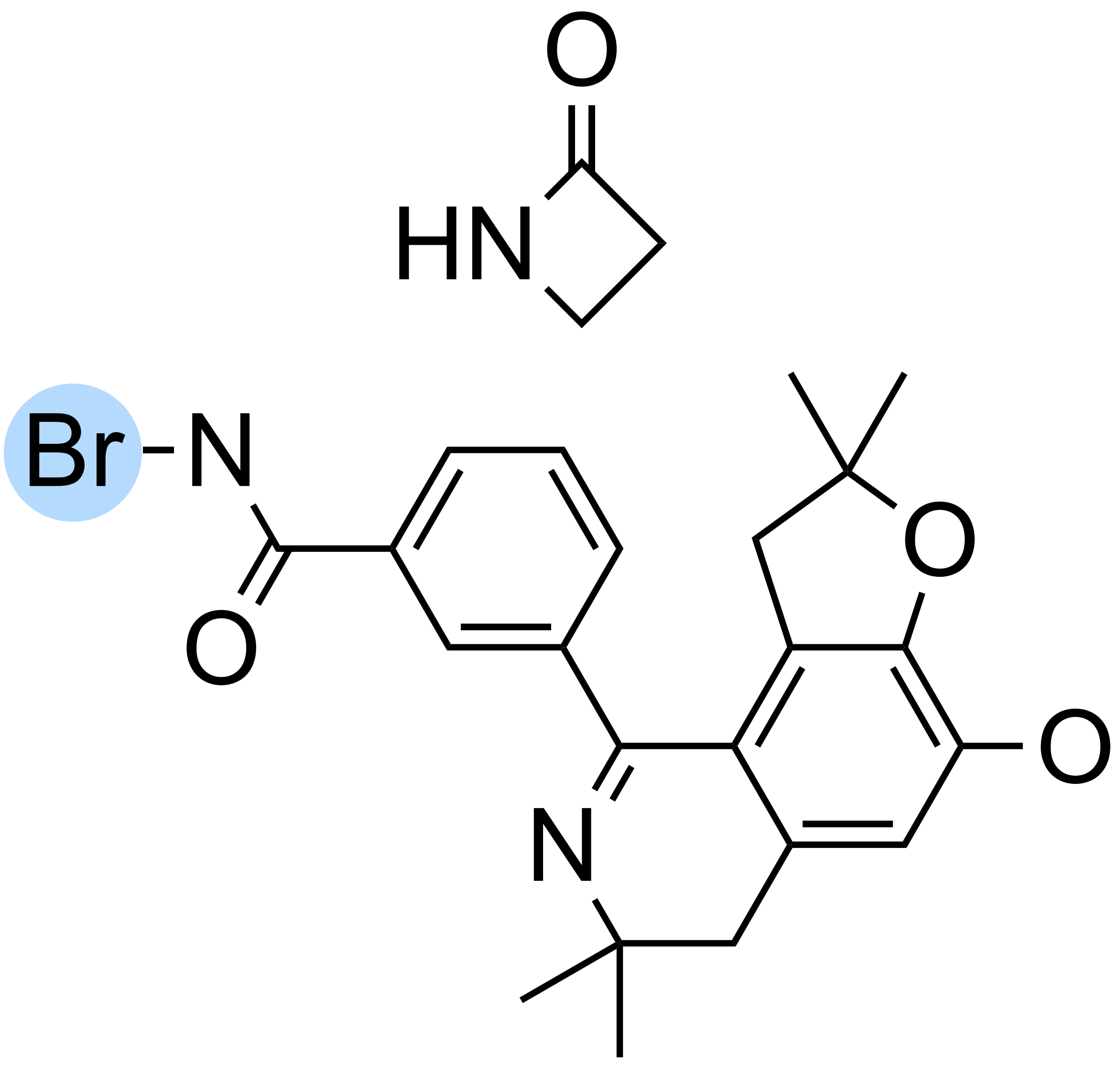
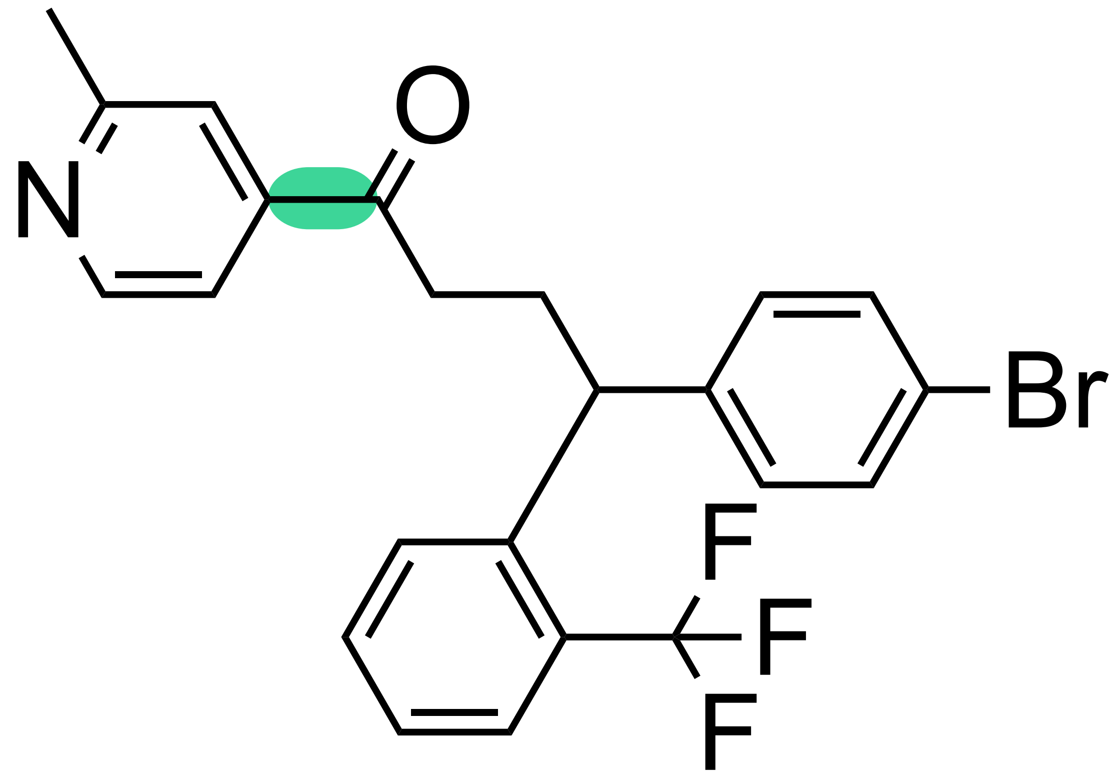


Predicted Reactants

🟦 leaving group 🟩 correct edit 🟥 incorrect edit

Example Predictions - Incorrect

Correct edit, but flipped leaving groups



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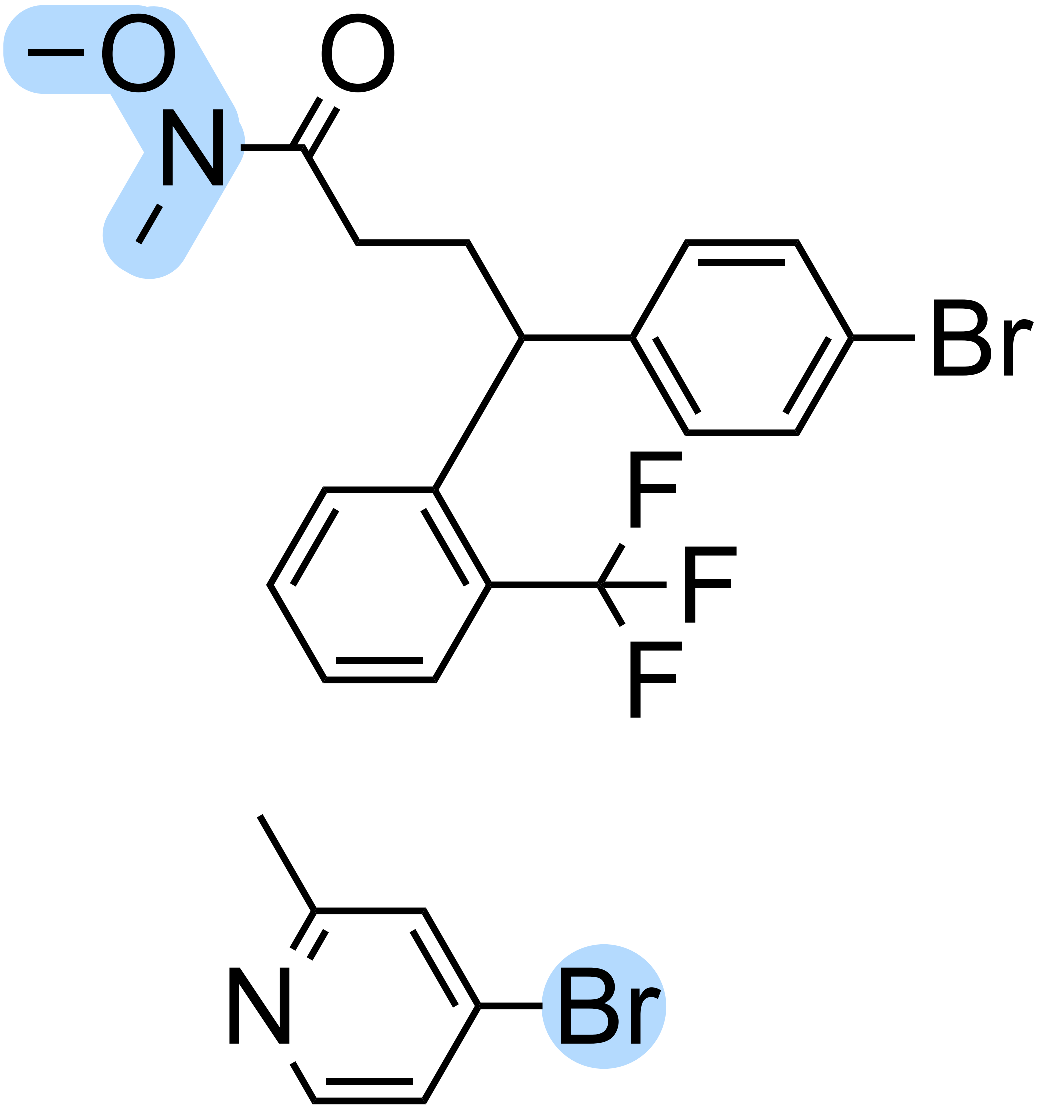

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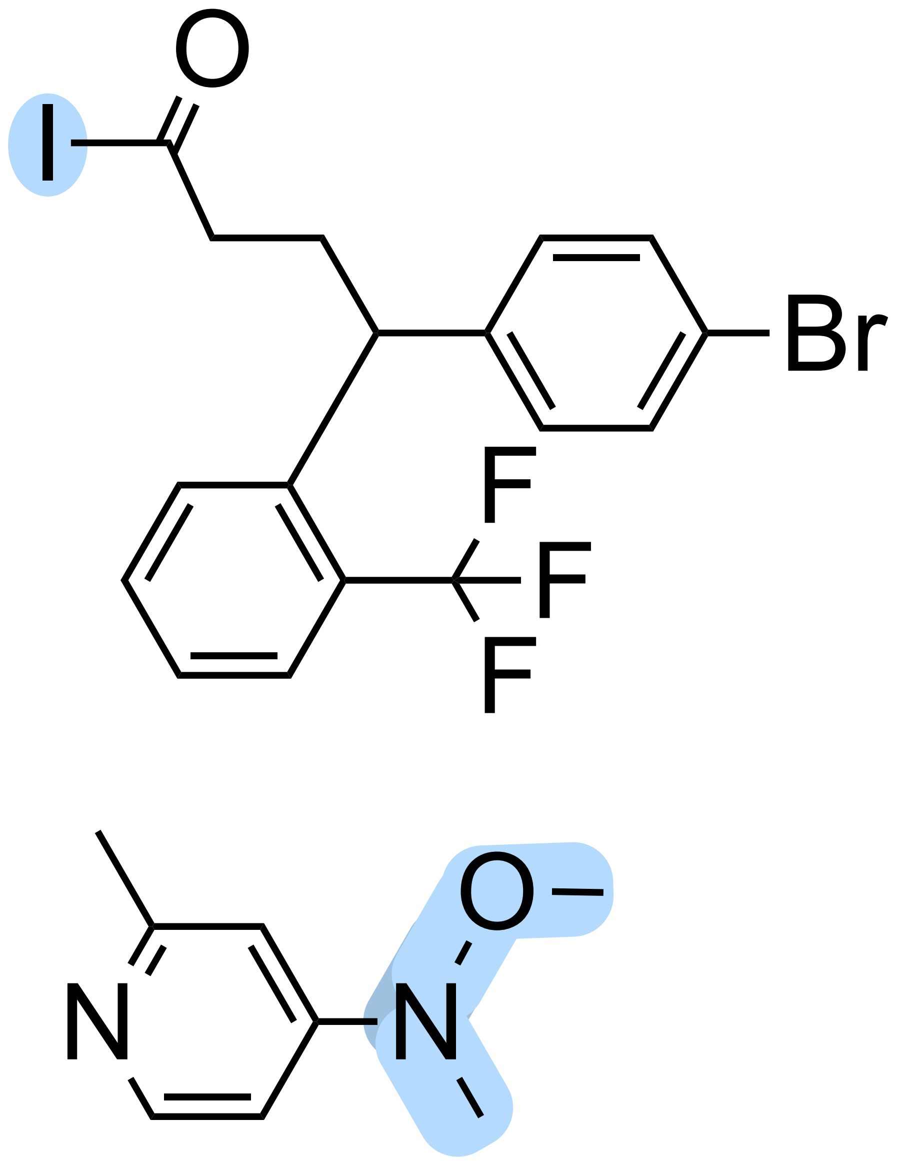

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Summary

- Propose a semi-template based method for retrosynthesis prediction
- Improves top-1 accuracy over previous semi-template methods and template-free methods

Future Work

- Edit prediction performance is a bottleneck to overall performance
  - Need more chemically meaningful priors and edit correction mechanisms
- Extend synthon completion to predict a single reactant from multiple reactants