SemiRetro: Semi-template framework boosts deep retrosynthesis prediction

Anonymous authors
Paper under double-blind review

Abstract

Retrosynthesis brings scientific and societal benefits by inferring possible reaction routes toward novel molecules. Recently, template-based (TB) and template-free (TF) molecule graph learning methods have shown promising results to solve this problem. TB methods are more accurate using pre-encoded reaction templates, and TF methods are more scalable by decomposing retrosynthesis into subproblems, i.e., center identification and synthon completion. To combine both advantages of TB and TF, we suggest breaking a full-template into several semi-templates and embedding them into the two-step TF framework. Since many semi-templates are reduplicative, the template redundancy can be reduced while the essential chemical knowledge is still preserved to facilitate synthon completion. We call our method SemiRetro and introduce a directed relational graph attention (DRGAT) layer to extract expressive features for better center identification. Experimental results show that SemiRetro significantly outperforms both existing TB and TF methods. In scalability, SemiRetro covers 96.9% data using 150 semi-templates, while previous template-based GLN requires 11,647 templates to cover 93.3% data. In top-1 accuracy, SemiRetro exceeds template-free G2G 3.4% (class known) and 6.4% (class unknown). Besides, SemiReto has better interpretability and training efficiency than existing methods.

1 Introduction

Retrosynthesis prediction (Corey & Wipke, 1969; Corey, 1991) plays a crucial role in synthesis planning and drug discovery, which aims to infer possible reactants for synthesizing a target molecule. This problem is quite challenging due to the vast search space, multiple theoretically correct synthetic paths, and incomplete understanding of the reaction mechanism, thus requiring considerable expertise and experience. Fortunately, with the rapid accumulation of chemical data, machine learning is promising to solve this problem (Coley et al., 2018; Segler et al., 2018). In this paper, we focus on the single-step version [1]: predicting the reactants from a given product.

Common deep-learning-based retrosynthesis works can be divided into template-based (TB) (Coley et al., 2017b; Segler & Waller, 2017; Dai et al., 2019) and template-free (TF) (Liu et al., 2017; Karpov et al., 2019) methods. Generally, TB methods achieve high accuracy by leveraging reaction templates, which encode the molecular changes during the reaction. However, the usage of templates brings some shortcomings, such as high computation cost and incomplete rule coverage, limiting the scalability. To improve the scalability, a class of chemically inspired TF methods (Shi et al., 2020; Yan et al., 2020) (see Fig. 1) have achieved dramatical success, which decompose retrosynthesis into subproblems: i) *center identification* and ii) *synthon completion*. Center identification increases the model scalability by breaking down the target molecule into virtual synthons without utilizing templates. Synthon completion simplifies reactant generation by taking synthons as potential starting molecules, i.e., predicting residual molecules and attaching them to synthons to get reactants. Although various TF methods have been proposed, the top-k retrosynthesis accuracy remains poor, especially when the reaction class is unknown. Can we find a more accurate way to predict potential reactants while keeping the scalability?

To address the aforementioned problem, we suggest combining the advantages of TB and TF approaches, and propose a novel framework namely SemiRetro. Specifically, we break a full-template

[1] In single-step retrosynthesis, the synthesis route length is 1, i.e., only one reaction needs to be inferred.

into several simpler semi-templates and embed them into the two-step TF framework. As many semi-templates are reduplicative, the template redundancy can be reduced while the essential chemical knowledge is still preserved to facilitate synthon completion. Moreover, we introduce a directed relational graph attention (DRGAT) layer to extract more expressive molecular features to improve center identification accuracy. Finally, we combine the center identification and synthon completion modules in a unified framework to accomplish retrosynthesis predictions.

We evaluate the effectiveness of SemiRetro on the benchmark data set USPTO-50k, and compare it with recent state-of-the-art TB and TF methods. We show that SemiRetro significantly outperforms these methods. In scalability, SemiRetro covers 96.9% of data using 150 semi-templates, while previous template-based GLN requires 11,647 templates to cover 93.3% of data. In top-1 accuracy, SemiRetro exceeds template-free G2G 3.4% (class known) and 6.4% (class unknown). Owing to the semi-template, SemiReto is more interpretable than template-free G2G and RetroXpert in synthon completion. Moreover, SemiRetro trains at least 6 times faster than G2G, RetroXpert, and GLN. All these results show that the proposed SemiRetro boosts the scalability and accuracy of deep retrosynthesis prediction.

2 Related work

Template-based models TB methods infer reactants from the product through shared chemical transformation patterns, namely reaction templates. These templates are either hand-crafted by human experts (Hartenfeller et al., 2011; Szymkuć et al., 2016) or automatically extracted by algorithms (Coley et al., 2017a; Law et al., 2009). For a product molecule, due to the vast search space, multiple qualified templates, and non-unique matching sites for each template, it is challenging to select and apply the proper template to generate chemically feasible reactants. To handle those challenges, (Coley et al., 2017b) suggests sharing the same templates among similar products. (Segler & Waller, 2017; Baylon et al., 2019) employ neural models for template selection with molecule fingerprint as input. The state-of-the-art GLN (Dai et al., 2019) learns the joint distribution of templates and products by decomposing templates into pre-reaction and post-reaction parts and introducing logic variables to apply structure constraints. TB methods are interpretable and accurate because they embed rich chemical knowledge into the algorithm. However, the vast space of templates and incomplete coverage severely limit their scalability.

Template-free models Instead of explicitly using templates, TF approaches learn chemical transformations by the model. (Liu et al., 2017; Karpov et al., 2019) solve the retrosynthesis problem with seq2seq models, e.g. Transformer (Vaswani et al., 2017), LSTM (Hochreiter & Schmidhuber, 1997), based on the SMILES representation of molecules. Despite the convenience of modeling, SMILES cannot fully utilize the inherent chemical structures and may generate invalid SMILES strings. Therefore, (Zheng et al., 2019) propose a self-corrected transformer to fix the syntax errors of candidate reactants. Recently, G2G (Shi et al., 2020), RetroXpert (Yan et al., 2020) and GraphRetro (Somnath et al., 2021) achieve state-of-the-art performance by decomposing the retrosynthesis into two sub-problems: i) center identification and ii) synthon completion, as shown in Fig. 1. Center identification increases the model scalability by breaking down the target molecule into virtual synthons without utilizing templates, among which G2G reports the highest accuracy. Synthon completion simplifies the complexity of reactant generation by taking synthons as potential starting molecules. For example, RetroXpert and G2G treat it as a SMILES or graph sequence translation problem from synthon to reactant. GraphRetro completes synthons by predicting pre-defined leaving groups, but it does not provide end-to-end open-source algorithms for attaching leaving groups and model construction. Generally, these TF methods are more scalable but perform worse than TB GLN in top-1 accuracy.

Challenges Although the two-step TF framework significantly improves the algorithm's scalability, the overall accuracy is relatively low. A possible solution to this issue is to enhance submodules, i.e., center identification and synthon completion. 1) To the best of our knowledge, current GNN models only work well for center identification when the reaction class is known; Otherwise, the model performance degrades rapidly. *How to develop a more suitable model that works well with unknown classes* is the first challenge. 2) In addition, synthon completion is the major bottleneck affecting the overall accuracy. Specifically, predicting and attaching residuals for each synthon are difficult because the residual structures could be complex, attaching residuals into synthons may violate chemical rules, and various residuals may agree with the same synthon (e.g., F, CI, Br, and I have similar chemical properties). For researchers, scalability, interpretability, and training efficiency are also important. *How to develop a more accurate, interpretable, and efficient synthon completion model while maintaining the scalability* is the second challenge.

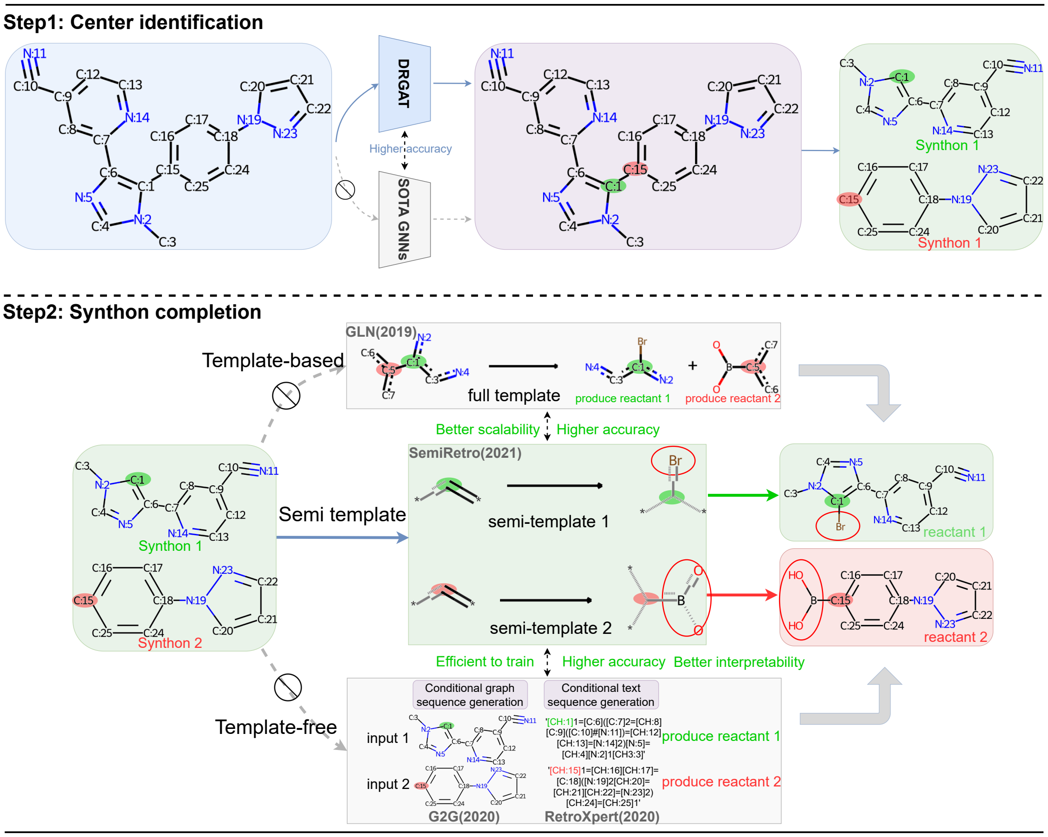


Figure 1: Overview of SemiRetro. We decomposite retrosynthesis into two steps: *center identification* and *synthon completion*. In step 1, we use DRGAT to extract molecule features for predicting reaction centers. By breaking product bonds in these centers, synthons can be obtained. In step 2, we use another DRGAT model to predict the semi-template for each synthon. The final reactants can be deduced from reaction centers, synthons, and semi-templates by using the residual attachment algorithm.

3 Definition and Overview

Molecule representation There are two types of dominant representations, i.e., SMILES string (Weininger, 1988) and molecular graph. SMILES is commonly used in early works (Liu et al., 2017; Schwaller et al., 2018; Zheng et al., 2019; Schwaller et al., 2019; Tetko et al., 2020) due to its simpleness. Many NLP models can be directly applied to solve related problems in an end-to-end fashion. However, these models cannot guarantee the chemical correctness of the output molecules because they ignore structure information to some extent. Similar to recent breakthroughs (Dai et al., 2019; Shi et al., 2020; Yan et al., 2020; Somnath et al., 2021), we take the molecule as a labeled graph $\mathcal{G}(A, X, E)$, where A, X and E are adjacency matrix, atom features and bond features, seeing Table. 1. Under the graph framework, we can effectively apply chemical constraints to ensure the validity of output molecules. Besides, graph-based methods are more controllable and interpretable than SMILES-based ones.

Problem definition Retrosynthesis aims to infer the set of reactants $\{\mathcal{R}_i\}_{i=1}^{N}$ that can generate the product $\mathcal{P}$. Formally, that is to learn a mapping function $\mathcal{F}_\theta$:

$$\mathcal{F}_\theta : \mathcal{P} \mapsto \{\mathcal{R}_i\}_{i=1}^{N_1}. \tag{1}$$

Considering the unknown by-products, the law of conservation of atoms no longer holds here, which makes the problem quite challenging because the algorithm needs to generate new atoms and bonds to get potential reactants automatically.

Overview As shown in Fig. 1, we adopt the two-step TF framework due to its scalability and effectiveness. Our method is distinguished from previous works in two folds: 1) We propose a relational graph attention (DRGAT) layer to improve the center identification performance; 2) We use semi-templates to facilitate synthon completion, which significantly reduces the problem complexity.

Table 1: Commonly used symbols

Symbol	Description
$\mathcal{G}(A, X, E)$	Molecular graph with adjacency matrix A, atom features X and bond features E.
A	$A \in \{0, 1\}^{n,n}$ with the number of atoms n. $a_{i,j} = 1$ indicates that there is a bond between atom i and j and vice versa.
X	$X \in \mathbb{R}^{n,d}$, d is the dimension of atom features. $\boldsymbol{x}_i$ is feature vector of atom i.
E	$E \in \mathbb{R}^{m,b}$, b is bond features dimension and m is the number of bonds.
$\boldsymbol{e}_{i,j}$	feature vector of bond (i, j).
$\mathcal{R}_i, \mathcal{S}_j, \mathcal{P}$	a molecular graph of the i-th reactant, the j-th synthon and the product.
c_i	$c_i \in \{0, 1\}$, indicating whether atom i is the reaction center or not.
$c_{i,j}$	$c_{i,j} \in \{0, 1\}$, indicating whether bond (i, j) is the reaction center or not.

4 Methodology

4.1 Center identification

Center identification plays a vital role in the two-step retrosynthesis because errors caused by this step directly lead to the final failures. Previous works have limitations, e.g., RetroXpert (Yan et al., 2020) provides incomplete prediction without considering atom centers, and G2G (Shi et al., 2020) performs poorly when the reaction class is unknown. How to obtain comprehensive and accurate center identification results is still worth exploring.

Reaction centers We consider both atom centers and bond centers in the product molecule. As shown in Fig. 2, from the product to its corresponding reactants, either some atoms add residuals by dehydrogenation without breaking the product structure (case 1), or some bonds are broken to allow new residues to attach (case 2). Both these atoms and bonds are called reaction centers.

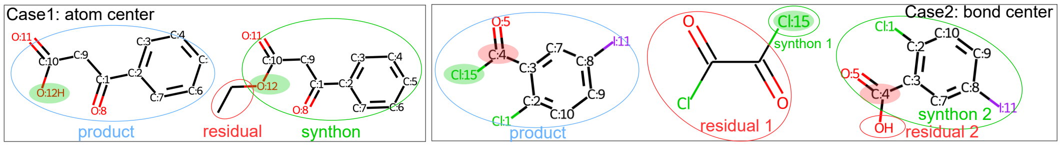
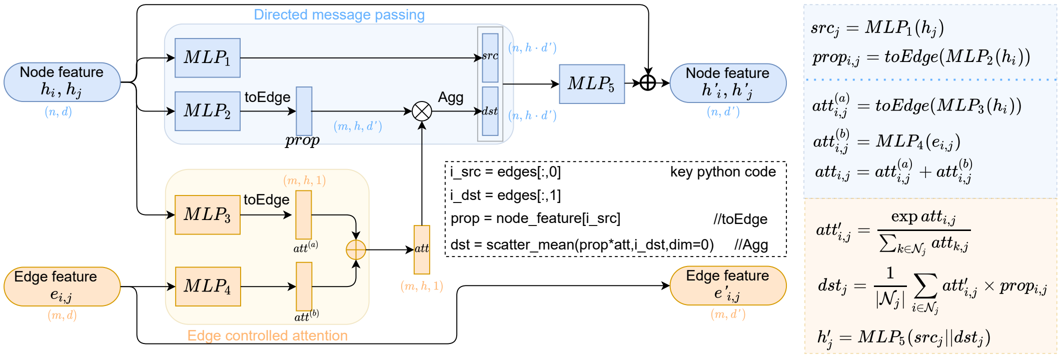


Figure 2: Reaction centers. Products, reactants, and residuals are circled in blue, green, and red, respectively. We label atoms in reaction centers with solid circles. In case 1, the centered atom adds residual by removing hydrogen atoms without changing the product structure. In case 2, the centered bond in the product is broken to generate synthons, to which new residuals are attached.

Directed relational GAT Commonly used graph neural networks (Defferrard et al., 2016; Kipf & Welling, 2016; Veličković et al., 2017) mainly focus on 0 and 1 edges, ignoring edge direction and multiple types, thus failing to capture expressive molecular features. As to molecules, different bonds represent different interatomic interactions, resulting in a multi-relational graph. Meanwhile, atoms at the end of the same bond may gain or lose electrons differently, leading to directionality. Considering these factors, we propose a directed relational graph attention (DRGAT) layer based on the general information propagation framework Zheng et al. (2021), as shown in Fig. 3. During message passing, DRGAT extracts source and destination node's features via independent MLPs to consider the bond direction and use the multi-head edge controlled attention mechanism to consider the multi-relational properties. We add shortcut connections from the input to the output in each layer and concatenate hidden representations of all layers to form the final node representation.



```
i_src = edges[:,0]
i_dst = edges[:,1]
prop = node_feature[i_src]                      //toEdge
dst = scatter_mean(prop*att,i_dst,dim=0)    //Agg
```

$$src_j = MLP_1(h_j)$$
$$prop_{i,j} = toEdge(MLP_2(h_i))$$
$$att^{(a)}_{i,j} = toEdge(MLP_3(h_i))$$
$$att^{(b)}_{i,j} = MLP_4(e_{i,j})$$
$$att_{i,j} = att^{(a)}_{i,j} + att^{(b)}_{i,j}$$
$$att'_{i,j} = \frac{\exp att_{i,j}}{\sum_{k \in \mathcal{N}_j} att_{k,j}}$$
$$dst_j = \frac{1}{|\mathcal{N}_j|} \sum_{i \in \mathcal{N}_j} att'_{i,j} \times prop_{i,j}$$
$$h'_j = MLP_5(src_j || dst_j)$$

Figure 3: DRGAT: Directed Relational GAT. DRGAT contains two submodules: directed message passing (DMP) and edge-controlled attention (ECA). DMP uses different MLP to learn features of the source (src) and target (dst) atoms during message passing. ECA utilizes both atom features and bond features to learn the attention weights.

Labeling and learning reaction centers We use the same labeling algorithm as G2G to identify ground truth reaction centers, where the core idea is comparing each pair of atoms in the product $\mathcal{P}$ with that in a reactant $\mathcal{R}_i$. We denote the atom center as $c_i \in \{0, 1\}$ and bond center as $c_{i,j} \in \{0, 1\}$ in the product $\mathcal{P}$. During the learning process, atoms features $\{\boldsymbol{h}_i\}_{i=1}^{|\mathcal{P}|}$ are learned from the product $\mathcal{P}$ by applying stacked DRGAT, and the input bond features are $\{\boldsymbol{e}_{i,j} | a_{i,j} = 1\}$. Then, we get the representations of atom i and bond (i, j) as

$$\underbrace{\hat{\boldsymbol{h}}_i = \boldsymbol{h}_i || \text{Readout}(\{\boldsymbol{h}_s\}_{s=1}^{|\mathcal{P}|})}_{\text{atom representation}} \quad \text{and} \quad \underbrace{\hat{\boldsymbol{h}}_{i,j} = \boldsymbol{e}_{ij} || \boldsymbol{h}_i || \boldsymbol{h}_j || \text{Readout}(\{\boldsymbol{h}_s\}_{s=1}^{|\mathcal{P}|})}_{\text{bond representation}}, \tag{2}$$

where we use average Readout operation, and $||$ is vector concatenation operation. Further, we predict the atom center probability p_i and bond center probability $p_{i,j}$ via MLPs:

$$p_i = \text{MLP}_6(\hat{\boldsymbol{h}}_i) \quad \text{and} \quad p_{i,j} = \text{MLP}_7(\hat{\boldsymbol{h}}_{i,j}). \tag{3}$$

Finally, center identification can be reduced to a binary classification, whose loss function is:

$$\mathcal{L}_1 = \sum_{\mathcal{P}} (\underbrace{\sum_i c_i \log p_i + (1 - c_i) \log p_i}_{\text{atom center}} + \underbrace{\sum_{i,j} c_{i,j} \log p_{i,j} + (1 - c_{i,j}) \log p_{i,j}}_{\text{bond center}}). \tag{4}$$

In summary, we propose a directed relational graph attention (DRGAT) layer to learn expressive atom and bond features for accurate center identification prediction. We consider both atom center and bond center to provide comprehensive results. In section. 5.2, we show that our method can achieve state-of-the-art accuracy, especially with reaction class unknown.

4.2 Synthon Completion

Synthon completion is the main bottleneck of two-step TF retrosynthesis, which is responsible for predicting and attaching residuals for each synthon. This task is challenging because the residual structures could be complex to predict, attaching residuals into synthons may violate chemical rules, and various residuals may agree with the same synthon. Because of these complexities, previous synthon completion approaches are usually inaccurate, unexplainable, and cumbersome. Introducing the necessary chemical knowledge to improve interpretability and accuracy can be a promising solution. However, how to provide attractive scalability and training efficiency is a new challenge.

Semi-templates The semi-template used in this paper is the local reaction pattern of each synthon, as shown in Fig. 4. Different from GraphRetro (Somnath et al., 2021), our semi-template contains not only residuals but also synthon's local structure. Similar to the work of forward reaction prediction (Segler & Waller, 2016), semi-template splits a binary reaction into two half reactions. Notably, we use dummy atom $*$ to represent possible synthon atoms that match the semi-template, significantly reducing redundancy. We extract semi-template from each synthon-reactant pair by removing reactant atoms that have exact matches in the synthon. There are two interesting observations: 1) Top-150 semi-templates cover 96.9% samples; 2) Reactants can be deterministically generated from semi-templates and synthons (introduced later). Based on these observations, synthon completion can be further simplified as a classification problem. In other words, we need to predict the semi-template type for each synthon, and the total number of classes is 150+1. The first 150 classes are top-150 semi-templates, and the 151st class indicates uncovered classes.

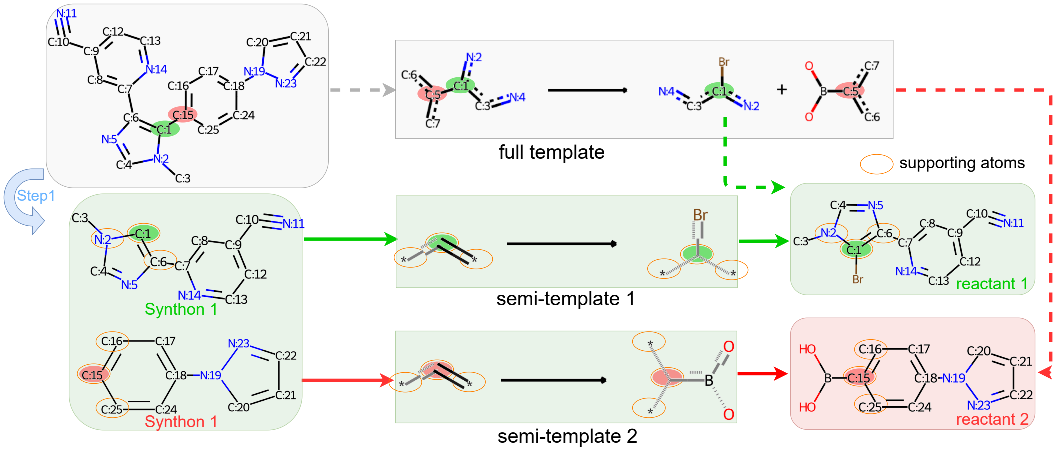


Figure 4: Semi-template vs. full-template. Semi-template is the local reaction template of each synthon. A full-template can be decomposed into several simpler semi-templates.

Learning semi-templates For each synthon $\mathcal{S}_j$, denote its semi-template label as $t_j, 1 \leq t_j \leq 151$. We use stacked DRGATs to extract atom features $\{\boldsymbol{h}_i\}_{i=1}^{|\mathcal{S}_j|}$ from $\mathcal{S}_j$. In each synthon, atoms that exactly match the semi-template are called supporting atoms, seeing circled atoms in Fig. 4. Given the supporting atom set $\{i_0, i_1, \cdots\}$, the semi-template representation is:

$$\hat{\boldsymbol{h}}_j = \text{Readout}(\{\boldsymbol{h}_i\}_{i=1}^{|\mathcal{S}_j|})||\text{Readout}(\{\boldsymbol{h}_k | k \in \{i_0, i_1, \cdots\}\}). \tag{5}$$

Based on this representation, we can get the predicted semi-template $\hat{t}_j$ as:

$$\hat{t}_j = \underset{1\leq c\leq 151}{\arg\max}\, \tilde{p}_{j,c}; \quad \tilde{\boldsymbol{p}}_j = \text{Softmax}(\text{MLP}_8(\hat{\boldsymbol{h}}_j)). \tag{6}$$

Denote $\mathbb{1}_{\{c\}}(\cdot)$ as the indicator function, the cross-entropy loss used for training is:

$$\mathcal{L}_2 = -\sum_{j\in\{1,2,\cdots,|\mathcal{S}|\}} \sum_{1\leq c\leq 151} \mathbb{1}_{\{c\}}(t_j)\log(\tilde{p}_{j,c}). \tag{7}$$

Applying semi-templates Once reaction centers, synthons, and corresponding semi-templates are known, we can deduce reactants with almost 100% accuracy. This is not a theoretical claim; We provide a practical residual attachment algorithm in the appendix and open source code on GitHub.

In summary, we suggest using the semi-templates to improve synthon completion performance. Firstly, reducing this complex task to a classification problem helps promote training efficiency and accuracy. Secondly, the high coverage of semi-templates significantly enhanced the scalability of TB methods. Thirdly, the deterministic residual attachment algorithm improves interpretability and accuracy. In section. 5.3, we will show the effectiveness of the proposed method.

5 Experiments

As mentioned earlier, the main contributions of this paper are proposing a DRGAT layer for central identification and suggesting to use semi-template for synthon completion. The effectiveness of the proposed method is evaluated by systematic experiments, which focus on answering these questions:

- **Q1:** For center identification (CI), how much performance gain can be obtained from DRGAT?
- **Q2:** For synthon completion (SC), can semi-templates reduce template redundancy and improve the synthon completion performance? And why?
- **Q3:** For retrosynthesis, how do we integrate CI and SC models into a unified retrosynthesis framework? Can SemiRetro outperform existing template-based and template-free methods?

5.1 Basic setting

Data We evaluate SemiRetro on the widely used benchmark dataset USPTO-50k (Schneider et al., 2016) to show its effectiveness. USPTO-50k contains 50k atom-mapped reactions with 10 reaction types. Following (Dai et al., 2019; Shi et al., 2020; Yan et al., 2020), the training/validation/test splits is 8:1:1. As mentioned in previous works, the USPTO-50k dataset contains a shortcut in that the product atom with atom-mapping ”1” is part of the reaction center in 75% of the cases. In our graph-based methods, this shortcut will not be introduced by forbidding atom position encoding.

Baselines Template-based GLN (Dai et al., 2019), template-free G2G (Shi et al., 2020) and RetroXpert (Yan et al., 2020) are primary baselines, which not only achieve state-of-the-art performance, but also provide open-source PyTorch code that allows us to verify their effectiveness. To show broad superiority, we also comapre SemiRetro with other baselines, incuding RetroSim (Coley et al., 2017b), NeuralSym (Segler & Waller, 2017), SCROP (Zheng et al., 2019), LV-Transformer (Chen et al., 2019), GraphRetro (Somnath et al., 2021), MEGAN (Sacha et al., 2021), and MHNreact (Seidl et al., 2021). As the retrosynthesis task is quite complex, subtle implementation differences or mistakes may cause critical performance fluctuations. We prefer comparing SemiReto with open-source methods whose results are more reliable. Energy-based approaches (Sun et al., 2020) are ignored because they are more like plug-and-play training strategies and result filters, focusing on enhancing existing models. For simplicity, we leave the use of energy function in the future and concentrate on comparing original retrosynthesis models.

Metrics This paper uses consistent metrics derived from previous literature for both submodule and overall performance. 1). *Center identification*: We report the accuracy of breaking input product into synthons. 2). *Synthon completion*: We present the accuracy of generating reactants from ground truth input synthons. When a product has multiple synthons, the final prediction is correct if and only if all reactants are correct. 3). *Retrosynthesis*: The metric is similar to that of synthon completion, except that the input synthons are also predicted by center identification. In other words, the retrosynthesis is correct if and only if both center identification and synthon completion are correct. Since there may be multiple valid routes for synthesizing a product, we report top-k accuracy.

Implementation details Thanks to the elegant implementation of G2G (Shi et al., 2020), we can develop our SemiRetro in a unified PyTorch framework (Paszke et al., 2019), namely TorchDrug. We use the same data preprocessing algorithm and code framework as G2G in center identification, ensuring the only difference is the GNN used for feature extraction. Besides, we use the open-source cheminformatics software RDkit (Landrum, 2016) to preprocess molecules and SMILES strings. The graph feature extractor consists of 6 stacked DRGAT, with the embedding size 256 for each layer. We train the proposed model for 30 and 100 epochs in center identification and synthon completion with batch size 64 on a single NVIDIA V100 GPU. The training costs of different methods can be found in the appendix. We run all experiments three times and report the means of their performance in default. To avoid the label leakage Yan et al. (2020); Somnath et al. (2021), we ignore atom mapping numbers during the training and evaluation phases.

5.2 Center identification (**Q1**)

Objective and setting This section studies how much center identification performance gain can be obtained from the proposed DRGAT, especially when the reaction class is unknown. The data preprocessing, training, and evaluating process is similar to G2G. The primary difference between our SemiRetro and G2G is the graph feature extractor, where we use DRGAT while G2G uses RGCN

(Schlichtkrull et al., 2018). We trained our model up to 30 epochs, which occupied about 2940 MB of GPU memory, where the batch size is 64, and the learning rate is 1e-5.

Results and analysis 1) **Highest accuracy**: As shown in 2, the proposed SemiRetro outperforms baselines on all the cases with different k. For example, SemiRetro achieves the highest top-1, top2, top-3, top-5 accuracy on both reaction class known and unknown settings. 2) **Better potential**: Since the possible synthesis routes toward a product may be multiple, the top-k accuracy ($k > 1$) is important, and the performance gain of SemiRetro rises as k increases, indicating the better potential. In particular, SemiRetro achieves nearly perfect top-5 accuracy on the setting of reaction class known (acc = 99.4%) and unknown (acc = 98.4%). 3) **Better adaptability**: In a more general and complex case, where the reaction class is unknown, SemiRetro can significantly exceed SOTA methods. For example, SemiRetro outperforms competitors by at least 10% on the top-3 and top-5 accuracy. These results show that the center identification performance has been dramatically improved using DRGAT, which is a good first step towards accurate retrosynthesis prediction.

	Top-k center identification accuracy							
	Reaction class known				Reaction class unknown			
k=	1	2	3	5	1	2	3	5
RetroXpert (Yan et al., 2020)	86.0	–	–	–	64.9	–	–	–
GraphRetro (Somnath et al., 2021)	84.6	92.2	93.7	94.5	70.8	85.1	89.5	92.7
G2G (Shi et al., 2020)	90.2	94.5	94.9	95.0	75.8	83.9	85.3	85.6
SemiRetro (our)	**90.9**	**97.2**	**98.5**	**99.4**	**80.5**	**92.8**	**96.0**	**98.4**
Improvement	+0.7	+2.7	+3.6	+4.4	+4.7	+8.9	+10.7	+12.8

Table 2: Top-k center identification accuracy. The best and sub-optimum results are highlighted in bold and underline.

5.3 Synthon completion (Q2)

Objective and setting This section reveals the effectiveness of using semi-template in three folds: 1) reducing the template redundancy, 2) improving the accuracy, and 3) promoting interpretability and training efficiency. Firstly, we count the full-templates of GLN and semi-templates introduced in this paper. We visualize the distribution and coverage of top-k templates for analyzing the redundancy. Secondly, we present the accuracy of synthon completion with ground truth synthon inputs. The final reactants are obtained by predicting the semi-templates and applying the residual attachment algorithm. Thirdly, we compare the interpretability and training efficiency of different methods in short. We trained our model up to 100 epochs, which occupied about 2320 MB of GPU memory, where the batch size is 64, and the learning rate is 1e-4.

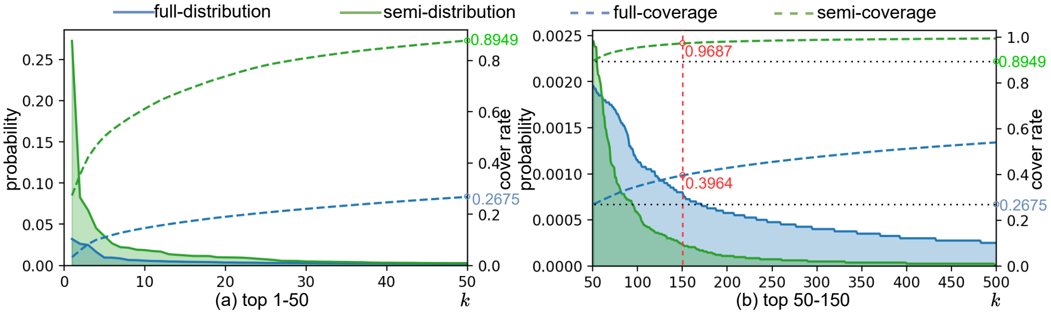


Figure 5: SemiRetro reduces the template redundancy.

	top-k synthon completion accuracy							
	Reaction class known				Reaction class unknown			
k=	1	3	5	10	1	3	5	10
G2G (Shi et al., 2020)	66.8	87.2	**91.5**	**93.9**	61.1	81.5	86.7	90.0
SemiRetro	**70.2**	**87.7**	**91.5**	93.2	**66.3**	**85.6**	**90.0**	**92.7**
Improvement	+3.4	+0.5	+0.0	–	+5.2	+4.1	+3.3	+2.7

Table 3: Top-k synthon completion accuracy.

Results and analysis (1) **Reduce redundancy**: In Fig. 5, we show the distribution and coverage of top-k full-templates and semi-templates, where the former distribution is sharper than the latter, indicating a higher top-k coverage. For example, the top-150 semi-templates cover the case of 96.87%, while the full-templates only cover 39.64%. Using semi-templates can reduce 11,647 full-templates into 150 semi-templates and increase the cover rate from 93.3% to 96.87%. (2) **Higher accuracy** As shown in Table. 3, SemiRetro outperforms G2G in most cases. This improvement comes from two parts: Firstly, semi-templates reduce the difficulty of predicting residual structures; Secondly, semi-templates eliminate the problem of residual attachment by using a deterministic algorithm. When the reaction class is unknown, the improvement is more dramatic. (3) **More interpretable and efficient** By using semi-templates, the residual attachment process is controllable and interpretable. In addition, our model can be trained at least 8 times faster than previous synthon completion models such as GLN, G2G, and RetroXpert, seeing the appendix for details.

5.4 RETROSYNTHESIS (**Q3**)

Objective and setting We explain how to combine center identification and synthon completion to provide end-to-end retrosynthesis predictions. We use a probability tree to search the top-k results, seeing Fig. 6, where the probability product of two-step predictions is used to rank these results.

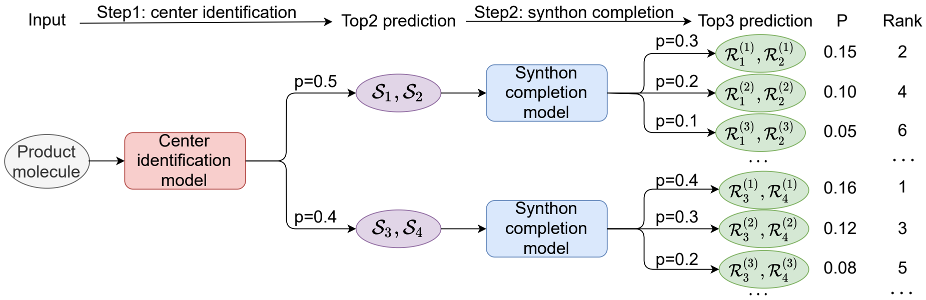

Input
Step1: center identification
Top2 prediction
Step2: synthon completion
Top3 prediction
P
Rank
Product molecule
Center identification model
p=0.5
p=0.4
$\mathcal{S}_1, \mathcal{S}_2$
$\mathcal{S}_3, \mathcal{S}_4$
Synthon completion model
Synthon completion model
p=0.3
p=0.2
p=0.1
p=0.4
p=0.3
p=0.2
$\mathcal{R}_1^{(1)}, \mathcal{R}_2^{(1)}$
$\mathcal{R}_1^{(2)}, \mathcal{R}_2^{(2)}$
$\mathcal{R}_1^{(3)}, \mathcal{R}_2^{(3)}$
$\mathcal{R}_3^{(1)}, \mathcal{R}_4^{(1)}$
$\mathcal{R}_3^{(2)}, \mathcal{R}_4^{(2)}$
$\mathcal{R}_3^{(3)}, \mathcal{R}_4^{(3)}$
0.15 2
0.10 4
0.05 6
0.16 1
0.12 3
0.08 5
...

Figure 6: The retrosynthesis example: combining top-2 CI and top-3 SC to obtain top-6 retrosynthesis results. Note that $\mathcal{S}_i$ indicates the i-th synthon, and $\mathcal{R}_i^{(j)}$ is the j-th predicted reactant of $\mathcal{S}_i$.

		top-k accuracy							
		Reaction class known				Reaction class unknown			
	k=	1	3	5	10	1	3	5	10
TB	RetroSim (Coley et al., 2017b)	52.9	73.8	81.2	88.1	37.3	54.7	63.3	74.1
	NeuralSym (Segler & Waller, 2017)	55.3	76.0	81.4	85.1	44.4	65.3	72.4	78.9
	GLN (Dai et al., 2019)	64.2	79.1	85.2	90.0	52.5	69.0	75.6	83.7
TF	SCROP (Zheng et al., 2019)	59.0	74.8	78.1	81.1	43.7	60.0	65.2	68.7
	LV-Transformer (Chen et al., 2019)	–	–	–	–	40.5	65.1	72.8	79.4
	G2G (Shi et al., 2020)	61.0	81.3	86.0	88.7	48.9	67.6	72.5	75.5
	RetroXpert (Yan et al., 2020)	62.1	75.8	78.5	80.9	50.4	61.1	62.3	63.4
	GraphRetro (Somnath et al., 2021)	63.9	81.5	85.2	88.1	53.7	68.3	72.2	75.5
	MEGAN (Sacha et al., 2021)	60.7	82.0	87.5	**91.6**	48.1	70.7	78.4	86.1
	MHNreact (Seidl et al., 2021)	–	–	–	–	50.5	73.9	81.0	**87.9**
Our	SemiRetro	**64.4**	**83.7**	**87.6**	90.2	**55.3**	**76.5**	**81.4**	85.4
	Improvement to GLN	+0.2	+4.6	+2.4	+0.2	+2.8	+7.5	+5.8	+1.7
	Improvement to G2G	+3.4	+2.4	+1.6	+1.5	+4.9	+8.9	+8.6	+6.0

Table 4: Overall performance. The best and sub-optimum results are highlighted in bold and underline. Only open source works participate in rigorous comparisons, such as GLN, G2G, and RetroXpert.

Results and analysis (1) **Higher accuracy**: SemiRetro achieves the highest accuracy in most settings, seeing Table. 4. As to previous works with open source code, template-free G2G and RetroXpert are more scalable than template-based GLN while sacrificing the top-1 accuracy. We use semi-template to reduce the template redundancy and improve the accuracy simultaneously. (2) **Better adaptability** We observe the performance gain of SemiRetro increases when the reaction class is unknown, suggesting our method can work better in more general and complex cases.

6 CONCLUSION

We propose SemiRetro for retrosynthesis prediction, which achieves better accuracy and attractive scalability than previous methods. Specifically, the DRGAT achieves the highest center identification accuracy. The semi-template improves both the accuracy and scalability of synthon completion. Moreover, SemiRetro has favorable interpretability and training efficiency. We hope this work will promote the development of deep retrosynthesis prediction.

REFERENCES

Javier L Baylon, Nicholas A Cilfone, Jeffrey R Gulcher, and Thomas W Chittenden. Enhancing retrosynthetic reaction prediction with deep learning using multiscale reaction classification. Journal of chemical information and modeling, 59(2):673–688, 2019.

Benson Chen, Tianxiao Shen, Tommi S Jaakkola, and Regina Barzilay. Learning to make generalizable and diverse predictions for retrosynthesis. arXiv preprint arXiv:1910.09688, 2019.

Connor W Coley, Regina Barzilay, Tommi S Jaakkola, William H Green, and Klavs F Jensen. Prediction of organic reaction outcomes using machine learning. ACS central science, 3(5):434–443, 2017a.

Connor W Coley, Luke Rogers, William H Green, and Klavs F Jensen. Computer-assisted retrosynthesis based on molecular similarity. ACS central science, 3(12):1237–1245, 2017b.

Connor W Coley, William H Green, and Klavs F Jensen. Machine learning in computer-aided synthesis planning. Accounts of chemical research, 51(5):1281–1289, 2018.

Elias James Corey. The logic of chemical synthesis: multistep synthesis of complex carbogenic molecules (nobel lecture). Angewandte Chemie International Edition in English, 30(5):455–465, 1991.

Elias James Corey and W Todd Wipke. Computer-assisted design of complex organic syntheses. Science, 166(3902):178–192, 1969.

Hanjun Dai, Chengtao Li, Connor Coley, Bo Dai, and Le Song. Retrosynthesis prediction with conditional graph logic network. Advances in Neural Information Processing Systems, 32:8872–8882, 2019.

Michaël Defferrard, Xavier Bresson, and Pierre Vandergheynst. Convolutional neural networks on graphs with fast localized spectral filtering. Advances in neural information processing systems, 29:3844–3852, 2016.

Markus Hartenfeller, Martin Eberle, Peter Meier, Cristina Nieto-Oberhuber, Karl-Heinz Altmann, Gisbert Schneider, Edgar Jacoby, and Steffen Renner. A collection of robust organic synthesis reactions for in silico molecule design. Journal of chemical information and modeling, 51(12): 3093–3098, 2011.

Sepp Hochreiter and Jürgen Schmidhuber. Long short-term memory. Neural computation, 9(8): 1735–1780, 1997.

Pavel Karpov, Guillaume Godin, and Igor V Tetko. A transformer model for retrosynthesis. In International Conference on Artificial Neural Networks, pp. 817–830. Springer, 2019.

Thomas N Kipf and Max Welling. Semi-supervised classification with graph convolutional networks. arXiv preprint arXiv:1609.02907, 2016.

Greg Landrum. Rdkit: Open-source cheminformatics software. 2016. URL https://github.com/rdkit/rdkit/releases/tag/Release_2016_09_4.

James Law, Zsolt Zsoldos, Aniko Simon, Darryl Reid, Yang Liu, Sing Yoong Khew, A Peter Johnson, Sarah Major, Robert A Wade, and Howard Y Ando. Route designer: a retrosynthetic analysis tool utilizing automated retrosynthetic rule generation. Journal of chemical information and modeling, 49(3):593–602, 2009.

Bowen Liu, Bharath Ramsundar, Prasad Kawthekar, Jade Shi, Joseph Gomes, Quang Luu Nguyen, Stephen Ho, Jack Sloane, Paul Wender, and Vijay Pande. Retrosynthetic reaction prediction using neural sequence-to-sequence models. ACS central science, 3(10):1103–1113, 2017.

Adam Paszke, Sam Gross, Francisco Massa, Adam Lerer, James Bradbury, Gregory Chanan, Trevor Killeen, Zeming Lin, Natalia Gimelshein, Luca Antiga, et al. Pytorch: An imperative style, high-performance deep learning library. Advances in neural information processing systems, 32: 8026–8037, 2019.

Mikołaj Sacha, Mikołaj Błaz, Piotr Byrski, Paweł Dabrowski-Tumanski, Mikołaj Chrominski, Rafał Loska, Paweł Włodarczyk-Pruszynski, and Stanisław Jastrzebski. Molecule edit graph attention network: modeling chemical reactions as sequences of graph edits. Journal of Chemical Information and Modeling, 61(7):3273–3284, 2021.

Michael Schlichtkrull, Thomas N Kipf, Peter Bloem, Rianne Van Den Berg, Ivan Titov, and Max Welling. Modeling relational data with graph convolutional networks. In European semantic web conference, pp. 593–607. Springer, 2018.

Nadine Schneider, Nikolaus Stiefl, and Gregory A Landrum. What's what: The (nearly) definitive guide to reaction role assignment. Journal of chemical information and modeling, 56(12):2336–2346, 2016.

Philippe Schwaller, Theophile Gaudin, David Lanyi, Costas Bekas, and Teodoro Laino. "found in translation": predicting outcomes of complex organic chemistry reactions using neural sequence-to-sequence models. Chemical science, 9(28):6091–6098, 2018.

Philippe Schwaller, Teodoro Laino, Théophile Gaudin, Peter Bolgar, Costas Bekas, et al. Molecular transformer for chemical reaction prediction and uncertainty estimation. 2019.

Marwin HS Segler and Mark P Waller. Modelling chemical reasoning to predict reactions. arXiv preprint arXiv:1608.07117, 2016.

Marwin HS Segler and Mark P Waller. Neural-symbolic machine learning for retrosynthesis and reaction prediction. Chemistry–A European Journal, 23(25):5966–5971, 2017.

Marwin HS Segler, Mike Preuss, and Mark P Waller. Planning chemical syntheses with deep neural networks and symbolic ai. Nature, 555(7698):604–610, 2018.

Philipp Seidl, Philipp Renz, Natalia Dyubankova, Paulo Neves, Jonas Verhoeven, Marwin Segler, Jörg K Wegner, Sepp Hochreiter, and Günter Klambauer. Modern hopfield networks for few-and zero-shot reaction template prediction. arXiv preprint arXiv:2104.03279, 2021.

Chence Shi, Minkai Xu, Hongyu Guo, Ming Zhang, and Jian Tang. A graph to graphs framework for retrosynthesis prediction. In International Conference on Machine Learning, pp. 8818–8827. PMLR, 2020.

Vignesh Ram Somnath, Charlotte Bunne, Connor W. Coley, Andreas Krause, and Regina Barzilay. Learning graph models for retrosynthesis prediction. In Thirty-Fifth Conference on Neural Information Processing Systems, 2021. URL `https://openreview.net/forum?id=SnONpXZ_uQ_`.

Ruoxi Sun, Hanjun Dai, Li Li, Steven Kearnes, and Bo Dai. Energy-based view of retrosynthesis. arXiv preprint arXiv:2007.13437, 2020.

Sara Szymkuć, Ewa P Gajewska, Tomasz Klucznik, Karol Molga, Piotr Dittwald, Michał Startek, Michał Bajczyk, and Bartosz A Grzybowski. Computer-assisted synthetic planning: the end of the beginning. Angewandte Chemie International Edition, 55(20):5904–5937, 2016.

Igor V Tetko, Pavel Karpov, Ruud Van Deursen, and Guillaume Godin. State-of-the-art augmented nlp transformer models for direct and single-step retrosynthesis. Nature communications, 11(1): 1–11, 2020.

Ashish Vaswani, Noam Shazeer, Niki Parmar, Jakob Uszkoreit, Llion Jones, Aidan N Gomez, Łukasz Kaiser, and Illia Polosukhin. Attention is all you need. In Advances in neural information processing systems, pp. 5998–6008, 2017.

Petar Veličković, Guillem Cucurull, Arantxa Casanova, Adriana Romero, Pietro Lio, and Yoshua Bengio. Graph attention networks. arXiv preprint arXiv:1710.10903, 2017.

David Weininger. Smiles, a chemical language and information system. 1. introduction to methodology and encoding rules. Journal of chemical information and computer sciences, 28(1):31–36, 1988.

Chaochao Yan, Qianggang Ding, Peilin Zhao, Shuangjia Zheng, JINYU YANG, Yang Yu, and Junzhou Huang. Retroxpert: Decompose retrosynthesis prediction like a chemist. In H. Larochelle, M. Ranzato, R. Hadsell, M. F. Balcan, and H. Lin (eds.), Advances in Neural Information Processing Systems, volume 33, pp. 11248–11258. Curran Associates, Inc., 2020. URL https://proceedings.neurips.cc/paper/2020/file/819f46e52c25763a55cc642422644317-Paper.pdf.

Qinkai Zheng, Houyi Li, Peng Zhang, Zhixiong Yang, Guowei Zhang, Xintan Zeng, and Yongchao Liu. Gipa: General information propagation algorithm for graph learning. arXiv preprint arXiv:2105.06035, 2021.

Shuangjia Zheng, Jiahua Rao, Zhongyue Zhang, Jun Xu, and Yuedong Yang. Predicting retrosynthetic reactions using self-corrected transformer neural networks. Journal of Chemical Information and Modeling, 60(1):47–55, 2019.

A APPENDIX

Center identification We show top-2 center identification predictions in Fig. 7, where synthons are obtained from breaking edge centers for downstream synthon completion. We present the probability of each prediction where the total probability of top-2 predictions exceeds 98%, indicating strong inductive confidence. Since the top-2 predictions are accurate enough, seeing Table. 2, we use them for synthon completion.

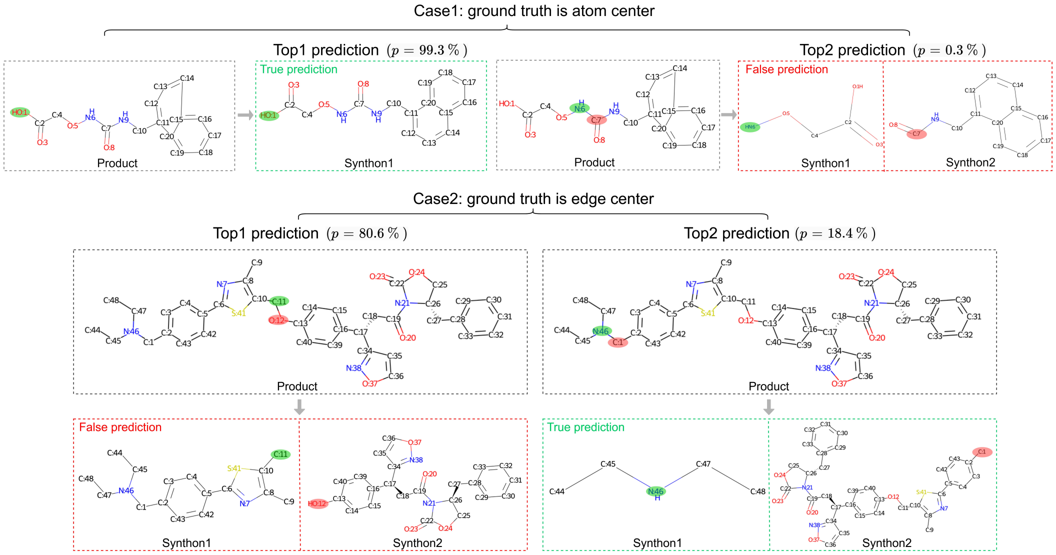
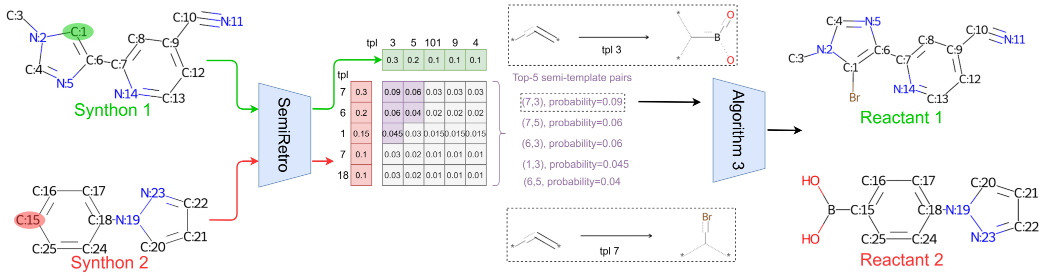

Case1: ground truth is atom center
Top1 prediction ($p = 99.3\,\%$)
Top2 prediction ($p = 0.3\,\%$)
True prediction
False prediction
Product
Synthon1
Synthon2
Case2: ground truth is edge center
Top1 prediction ($p = 80.6\,\%$)
Top2 prediction ($p = 18.4\,\%$)

Figure 7: Visualize results of center identification. Case1: the ground truth is atom center, and the top-1 prediction is correct with the probability 99.3%. Case2: The ground truth is edge center, and the top-2 prediction is correct with the probability 18.4%.

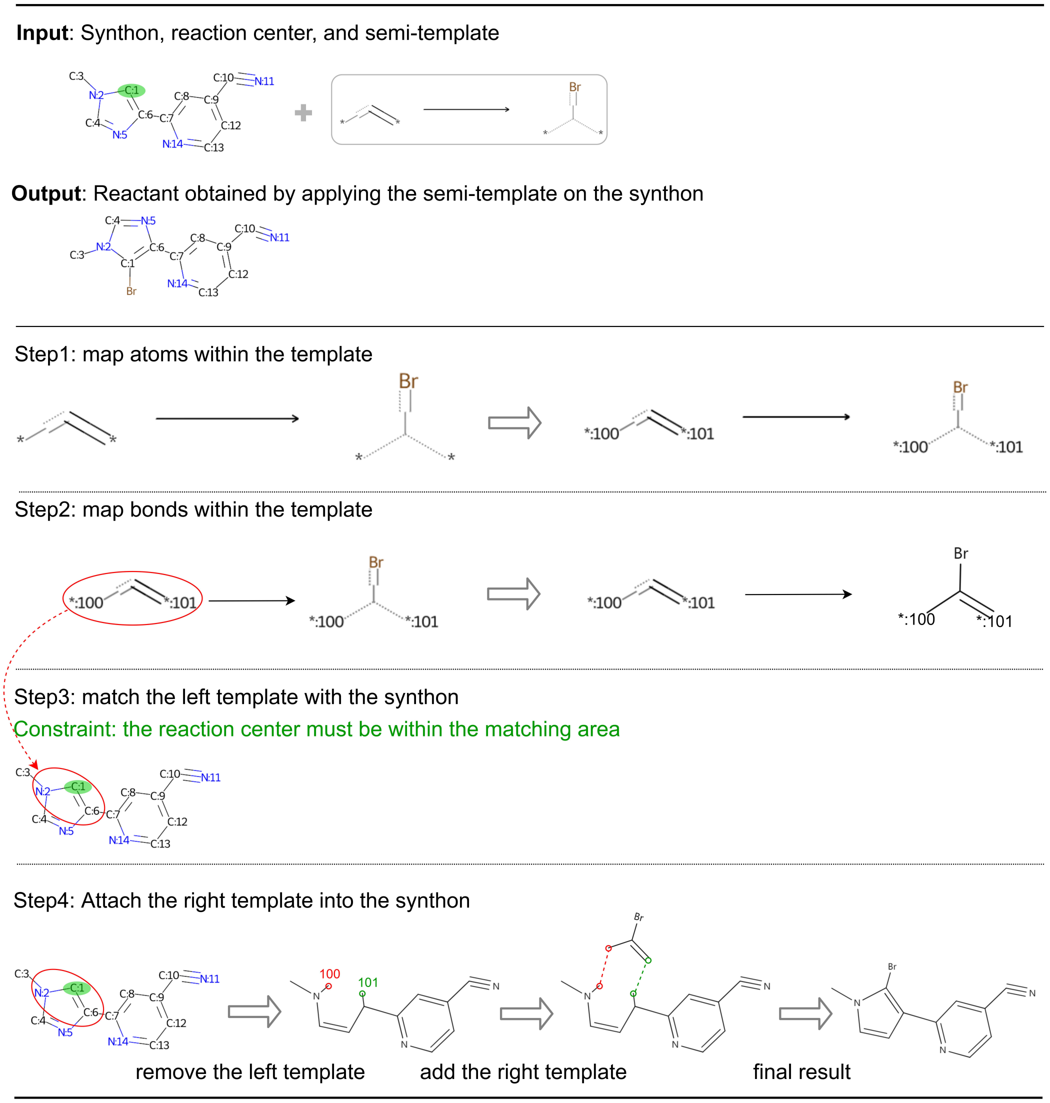
Synthon completion In Fig. 8, we present the process of predicting multiple reactants of the same product. This process provides an end-to-end view of synthon completion, containing semi-template prediction, top-k results search, and semi-template application. By default, we choose the top-5 synthon completion results for each center identification output as part of the final top-10 retrosynthesis results.



tpl		3	5	101	9	4
		0.3	0.2	0.1	0.1	0.1
7	0.3	0.09	0.06	0.03	0.03	0.03
6	0.2	0.06	0.04	0.02	0.02	0.02
1	0.15	0.045	0.03	0.015	0.015	0.015
7	0.1	0.03	0.02	0.01	0.01	0.01
18	0.1	0.03	0.02	0.01	0.01	0.01

Figure 8: The overall pipeline of synthon completion. The input synthons are the outputs of the center identification module, coming from the same product molecule. We get the top-5 semi-template predictions and their probabilities of each synthon using SemiRetro (synthon completion network), then generate the joint distribution of semi-templates. We choose the top-5 predictions from this joint distribution and apply the residual attachment algorithm (introduced later) to get the final reactants.

Table 5: Residual attachment algorithm. For easy and quick understanding, we demonstrate the core idea by visual samples. The detailed implementation can be found in the open-source code.


Input: Synthon, reaction center, and semi-template
Output: Reactant obtained by applying the semi-template on the synthon
Step1: map atoms within the template
*:100
*:101
Br
Step2: map bonds within the template
Step3: match the left template with the synthon
Constraint: the reaction center must be within the matching area
Step4: Attach the right template into the synthon
100
101
remove the left template
add the right template
final result

Platform The platform for our experiment is ubuntu 18.04, with a Intel® Xeon® Gold 6240R Processor and 256GB memory. We use a single NVIDIA V100 to train models, where the CUDA version is 10.2.

	Retrosynthesis	Center identification			Synthon completion		
	GLN	RetroXpert	G2G	SemiRetro	RetroXpert	G2G	SemiRetro
time/epoch	785s	440s	58s	**48s**	330s	322s	**40s**
GPU memory/sample	274.7MB	55.7MB	46.1MB	**45.9MB**	147.7MB	65.7MB	**36.3MB**
total epochs	50	80	100	30	300	100	100

Table 6: The training costs of different methods. We run the open-source code of these methods on the same platform, reporting the training time per epoch and occupied GPU memory per sample. We also show the total training epochs mentioned in their paper (preferred) or code. If the author reports training steps, we calculate $\text{epochs}_{\text{total}} = \text{steps}_{\text{total}}/\text{steps}_{\text{interval}}$.

Important details We follow the setting of G2Gs, which provides open-source code on https://github.com/DeepGraphLearning/torchdrug/. G2Gs use different atom features in their open-source code for center identification and synthon completion. In this paper, we use the same atom features of G2Gs. We have also tried to combine all these atom features and use the same set of features in center identification and synthon completion models. The combined atom features do not make a significant difference.

Name	Description
Atom type	Type of atom (ex. C, N, O), by atomic number
# Hs	one-hot embedding for the total number of Hs (explicit and implicit) on the atom
Degree	one-hot embedding for the degree of the atom in the molecule including Hs
Valence	one-hot embedding for the total valence (explicit + implicit) of the atom
Aromaticity	Whether this atom is part of an aromatic system.
Ring	whether the atom is in a ring

Table 7: Atom features for center identification.

Name	Description
Bond type	one-hot embedding for the type of the bond
Bond direction	one-hot embedding for the direction of the bond
Stereo	one-hot embedding for the stereo configuration of the bond
Conjugation	whether the bond is considered to be conjugated
Bond length	the length of the bond

Table 8: Bond features for center identification.

Name	Description
Atom type	Type of atom (ex. C, N, O), by atomic number
# Hs	one-hot embedding for the total number of Hs (explicit and implicit) on the atom
Degree	one-hot embedding for the degree of the atom in the molecule including Hs
Ring	whether the atom is in a ring
Ring 3	whether the atom is in a ring of size 3
Ring 4	whether the atom is in a ring of size 4
Ring 5	whether the atom is in a ring of size 5
Ring 6	whether the atom is in a ring of size 6
Ring 6+	whether the atom is in a ring of size larger than 6

Table 9: Atom features for synthon completion. Note that synthon completion do not use bond features.