Self-Improved Retrosynthetic Planning

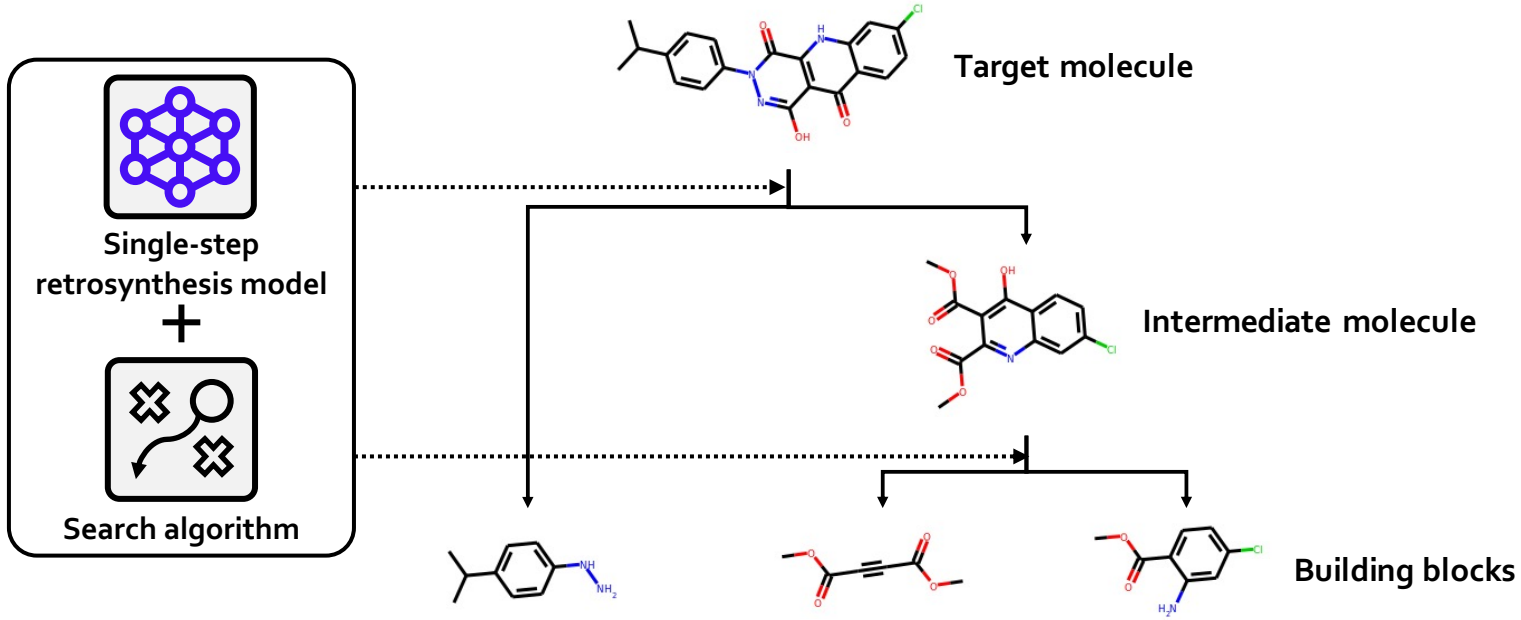
Junsu Kim[1] (presenter), Sungsoo Ahn[2], Hankook Lee[1], and Jinwoo Shin[1]

[1]Korea Advanced Institute of Science and Technology (KAIST)

[2]Mohamed bin Zayed University of Artificial Intelligence (MBZUAI)

Background: Retrosynthetic Planning

- Goal: finding a series of chemically valid reactions starting from target molecule until reaching the building block molecules.
  - In a backward and recursive manner.
  - Crucial in drug discovery and material design.



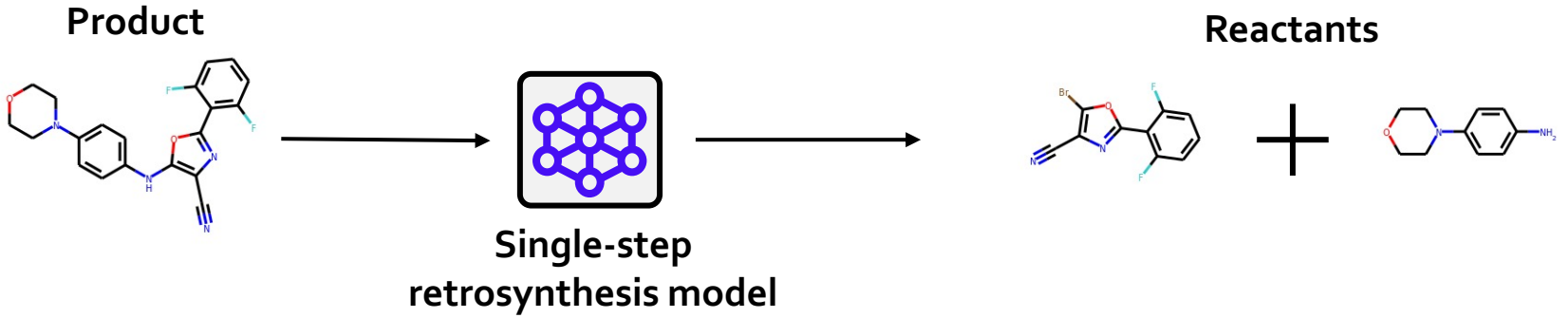
Retrosynthetic planning

Background: Retrosynthetic Planning

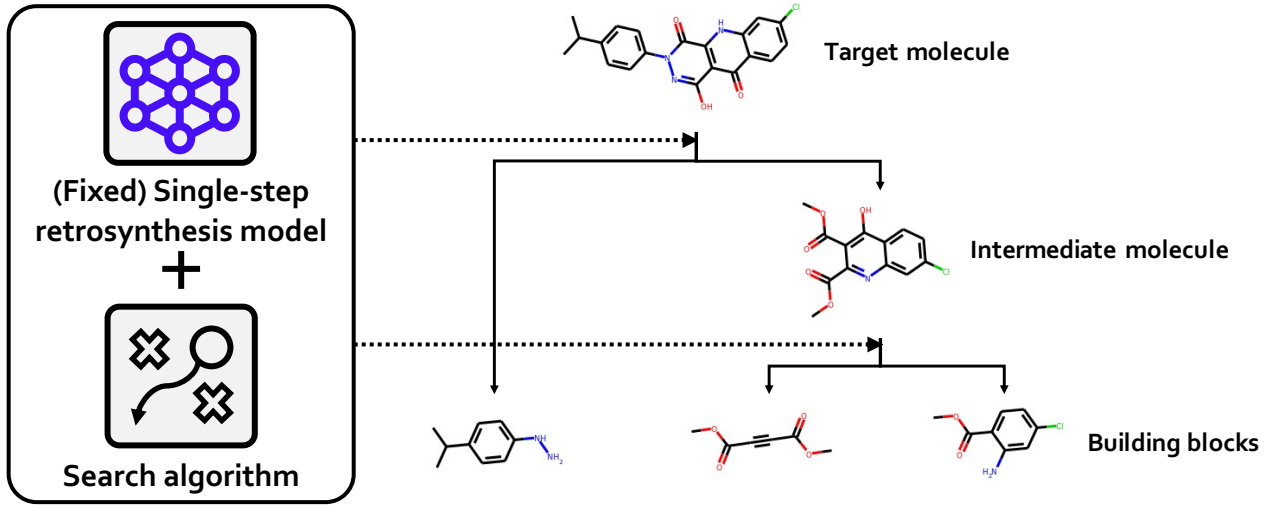
- The main **challenge** of retrosynthetic planning is twofold:
  - (a) Finding an **accurate single-step retrosynthesis model**.
    - Why? To guarantee chemical validity of searched pathways.
  - (b) Designing an **efficient search algorithm**.
    - Why? The search space is huge due to the vast number of possible chemical reactions.

Background: Retrosynthetic Planning

- Most of existing works are **two-stage** framework.
  - **Stage 1. Train single-step retrosynthesis model** parameterized by deep neural networks (DNN).



  - **Stage 2.** Run **search algorithms** with the trained DNN-based single-step retrosynthesis model.



Our approach

- The existing two-stage frameworks are **suboptimal**.
  - DNN-based single-step retrosynthesis model **only** considers the requirement **(a)**, **not (b)**.
    - **(a)** Reaction pathways should be **represented by real-world reactions**.
    - **(b)** Reaction pathways should be **executable using "building block" molecules**.

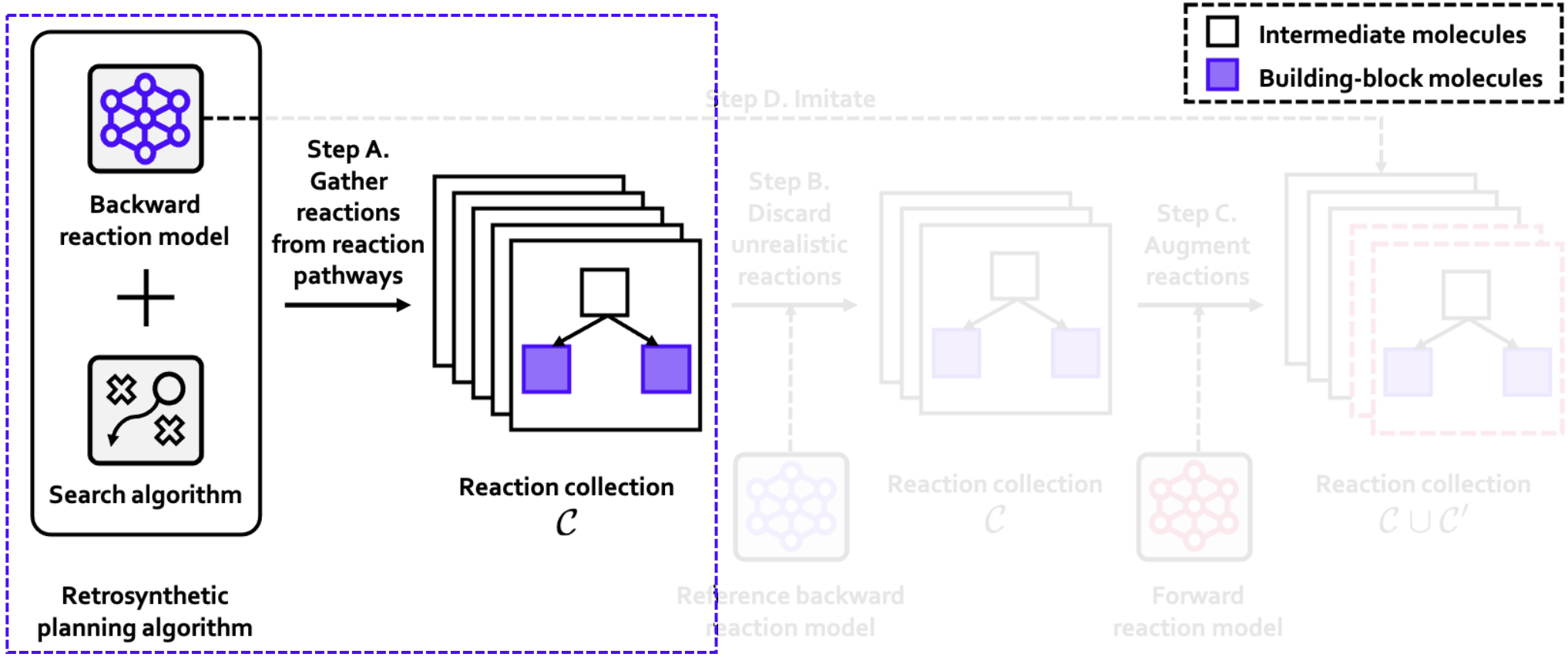
- Motivated by this, **we propose an end-to-end framework**.
  - **Directly training the DNNs** towards generating reaction pathways with **both** properties **(a)** and **(b)**.

Our approach

- Key idea: **self-improving procedure** that trains *backward reaction model* (i.e., single-step retrosynthesis model) **to imitate successful pathways found by itself**.

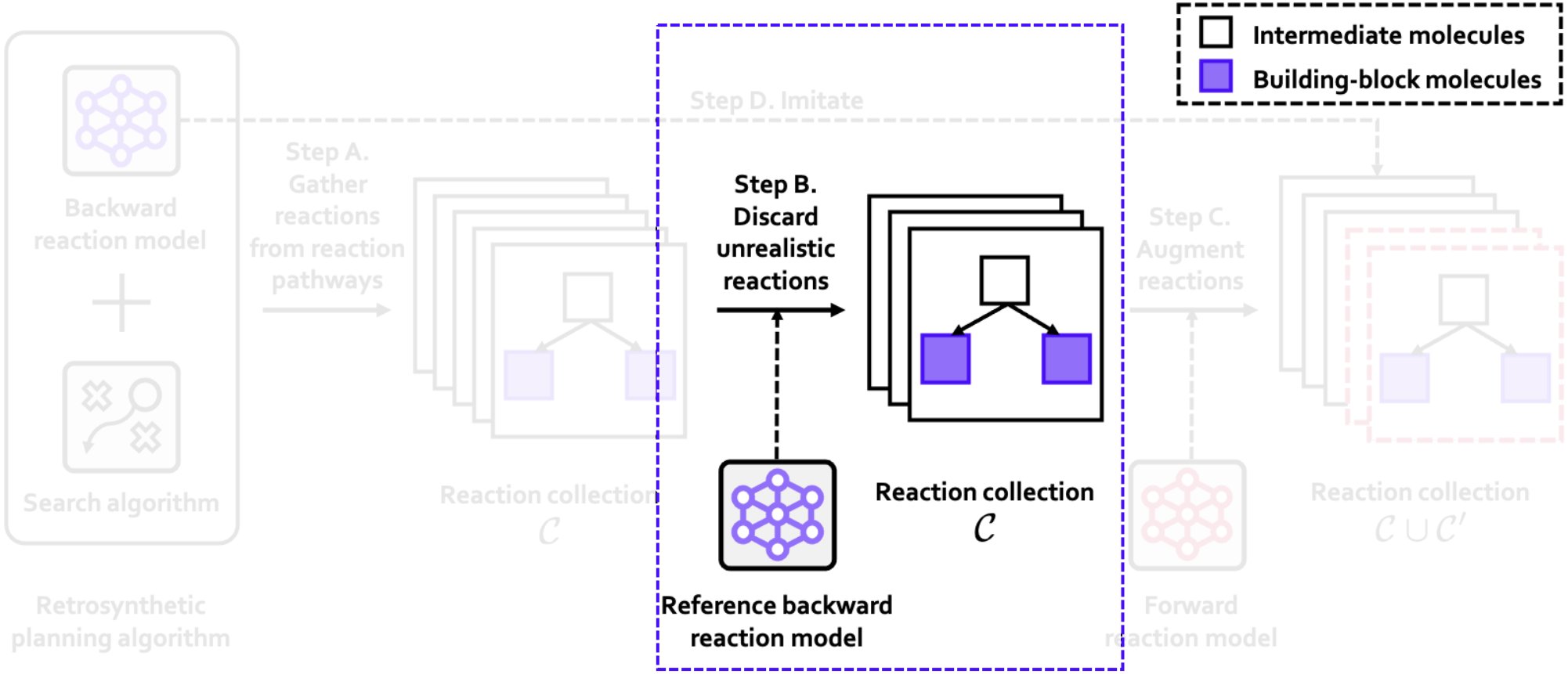
Our approach

- **Step A**. **Gather reactions from reaction pathways** found by search algorithm combined with the backward reaction model.



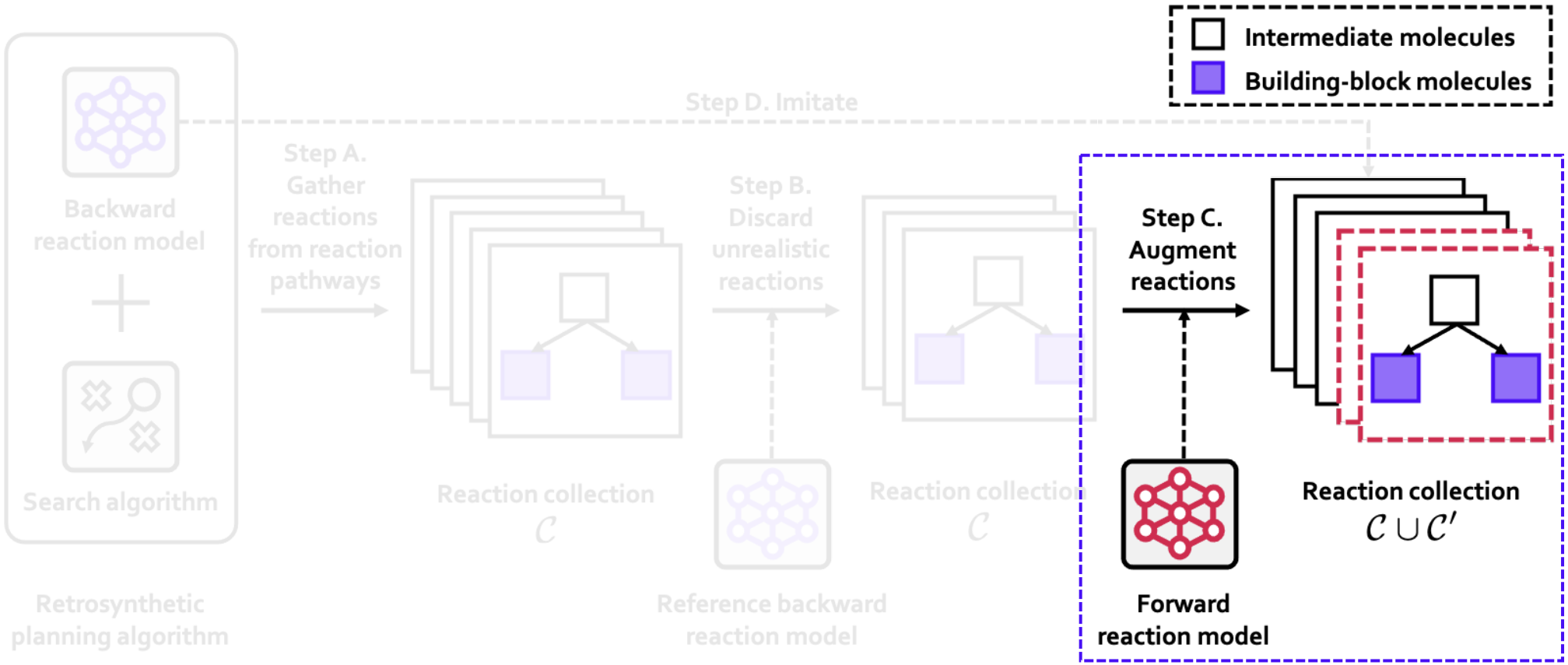
Our approach

- **Step B. Discard unrealistic reactions** using a *reference backward reaction model.*
  - *Reference backward reaction model* determines whether a reaction resembles real-world reactions.



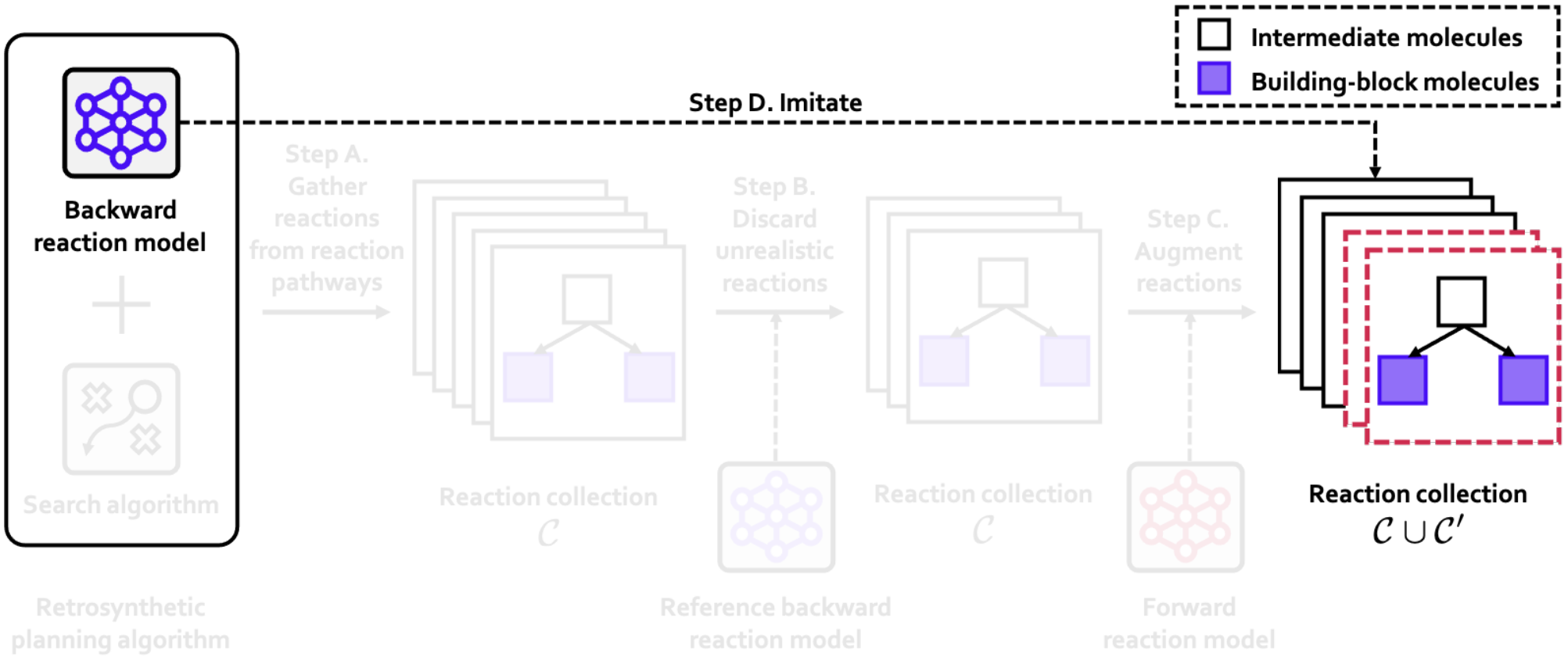
Our approach

- **Step C**. **Augment reactions** via a *forward reaction model* (i.e., single-step synthesis model).



Our approach

- **Step D**. Train the backward reaction model to **imitate** the generated reactions.



Our approach (in detail)

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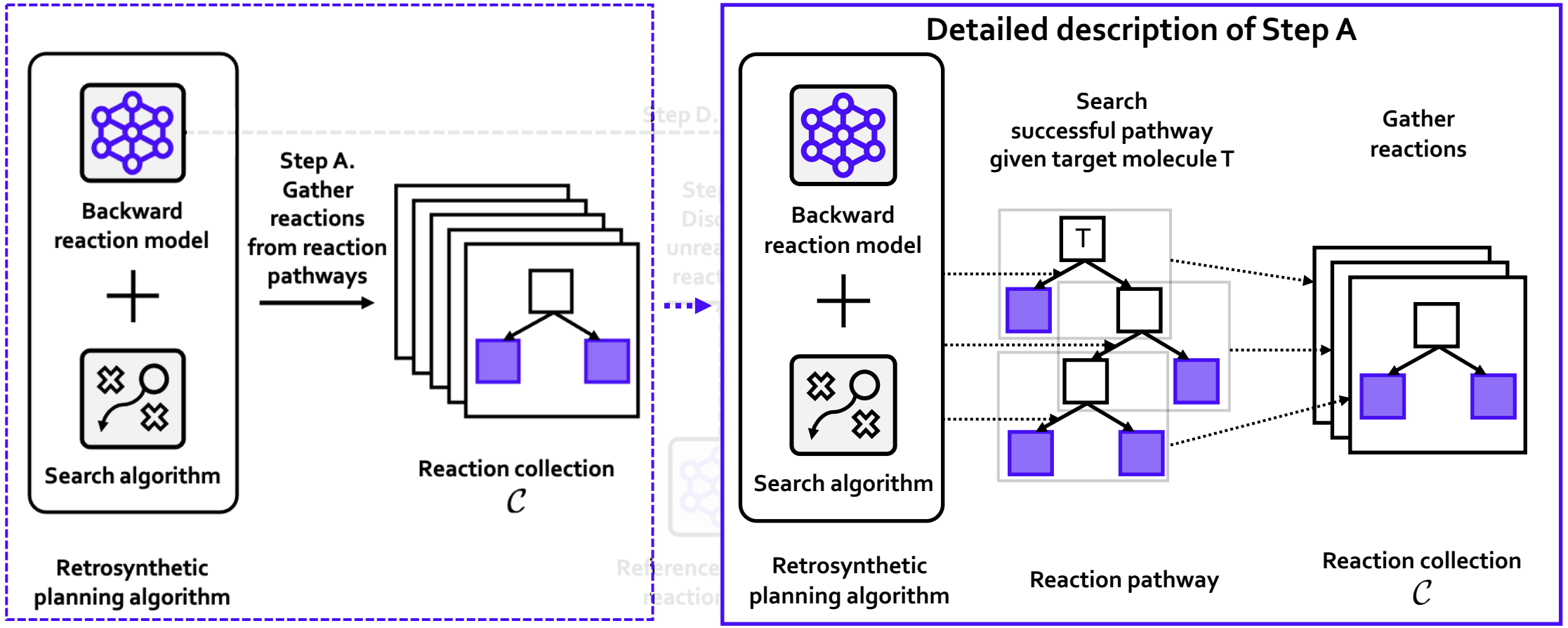

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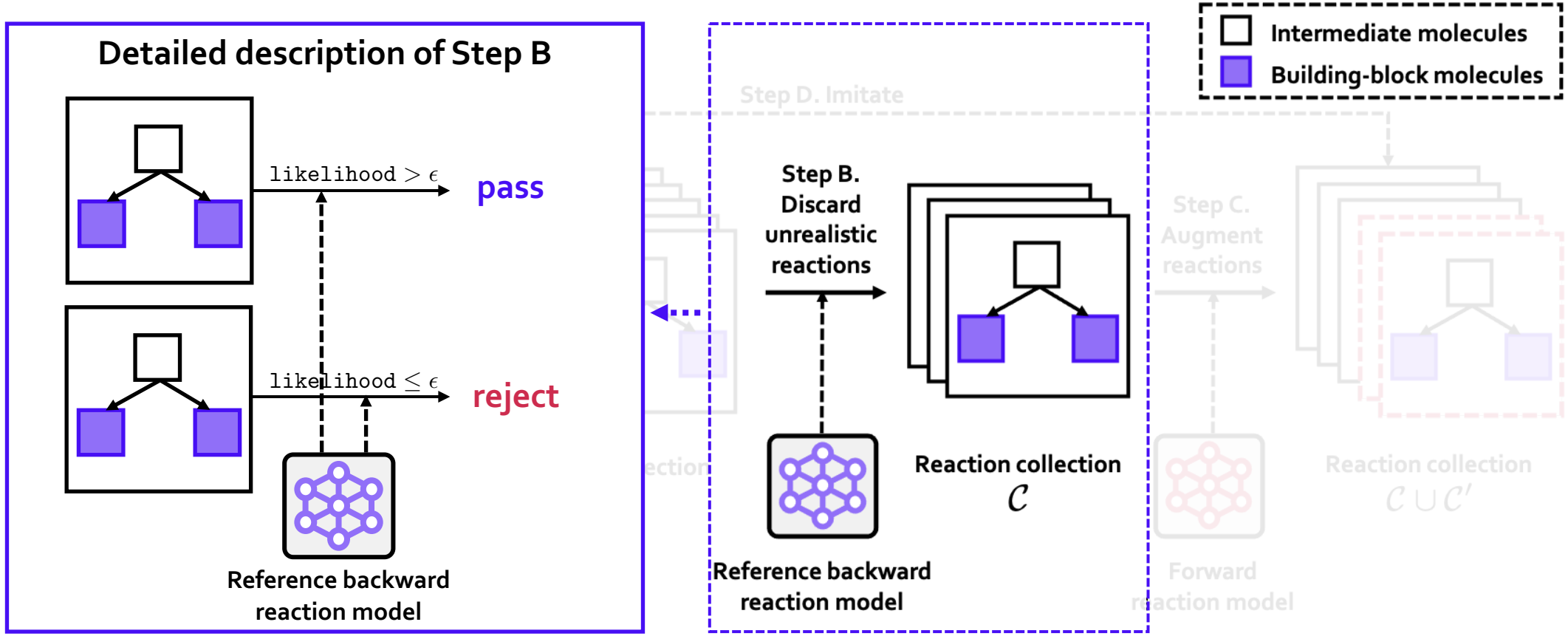
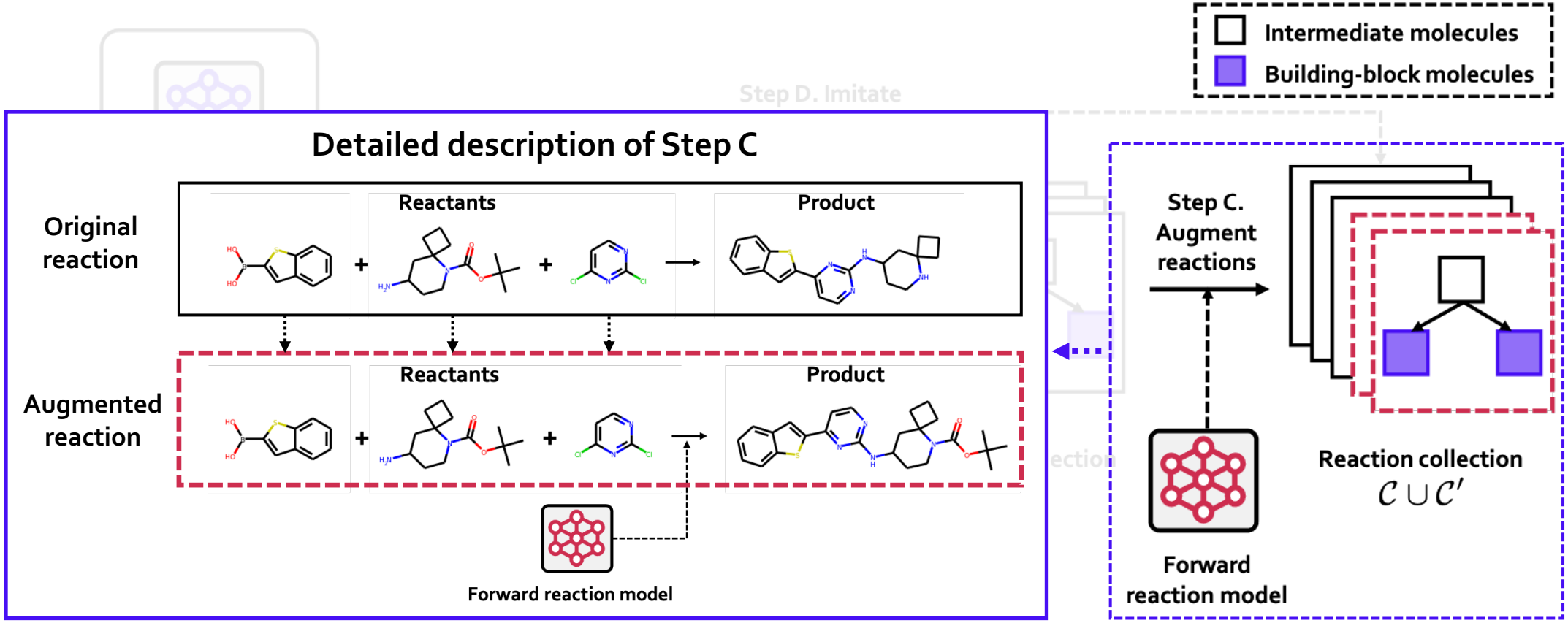


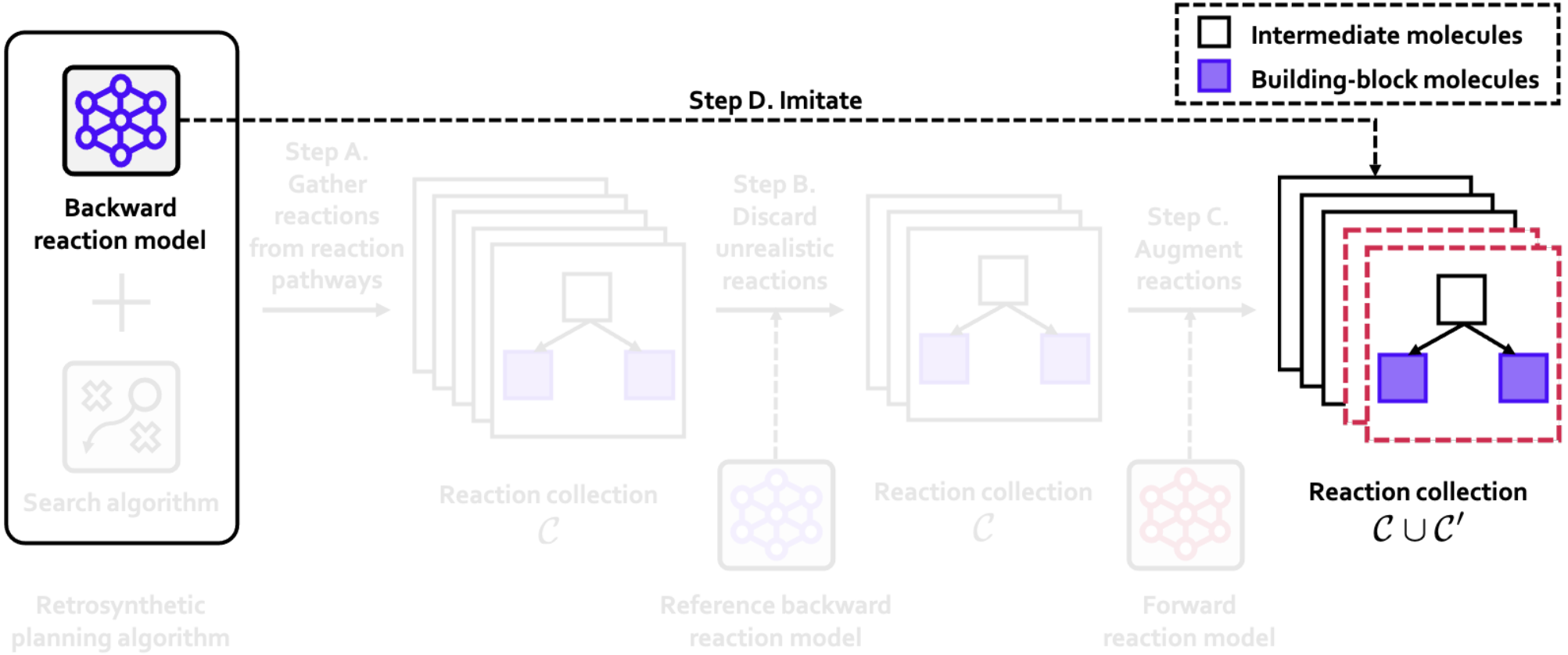
Our approach (in detail)

- **Step C**. **Augment reactions** via a *forward reaction model* (i.e., single-step synthesis model).
  - Based on the knowledge; there can be **multiple products** resulting from the **same reactant-set**.



Our approach (in detail)

- **Step D**. Train the backward reaction model by maximizing the log-likelihood of the reactions in $\mathcal{C} \cup \mathcal{C}'$.



Experiments

- Our framework achieves the **state-of-the-art performance**.
  - Ours improves success rate from 86.84% to 96.32%.
  - Search time, length and cost of searched pathways are improved.
  - Backward reaction model maintains its reliability.

Algorithm	Reactions		Reaction pathways				
	Top-1 ↑	Top-10 ↑	Succ. rate ↑ ($N = 50$)	Succ. rate ↑ ($N = 500$)	Length ↓	Time ↓	Cost ↓
Greedy DFS†	-	-	-	22.63	-	388.15	-
MCTS†	-	-	-	33.68	-	370.51	-
DFPN-E†	-	-	-	55.26	-	279.67	-
Retro*-0	**44.53**	72.71	27.37	79.47	11.21	208.09	19.40
Retro*-0 + ours	44.03 (-1.12%)	73.14 (+0.59%)	57.37 (+109.62%)	**96.32** (+21.20%)	**7.69** (-31.40%)	**96.22** (-53.76%)	**11.66** (-39.90%)
Retro*	**44.53**	72.71	44.21	86.84	9.71	157.11	15.33
Retro* + ours	44.03 (-1.12%)	**73.15** (+0.61%)	**57.89** (+30.94%)	91.05 (+4.85%)	8.74 (-9.99%)	100.15 (-36.25%)	15.23 (-0.65%)

Conclusion

- We propose an **end-to-end framework** based on **self-improved model adaptation** to improve retrosynthetic planning.

- We also propose an additional **reaction augmentation** scheme.

- Our work **reduces the gap** between supervised learning of **single-step retrosynthesis models** and the goal of **retrosynthetic planning**.