Supplementary Information

Table S1 Configuration settings for different search algorithm variants

Parameter	Retro*	MCTS	All-Routes-Retro*	All-Routes-MCTS
Expansion Top-k	50	50	50	50
Max Transforms	30	30	30	30
Iteration Limit	25,000	500	25,000	500
Time Limit	8 hours	8 hours	2 hours	2 hours
Return Found Route	First	First	All	All

Table S2 AffinityPropagation Settings

Parameter	Value
Damping	0.9
Max Iterations	500
Convergence Iterations	30
Preference	-50

Table S3 Synthesis route average statistics for different search algorithms on the ChEMBL100 dataset

Algorithm	Solved Molecules	Avg. Solved Routes	Avg. Reactions in Shortest Route	Avg. Distance between 100 Shortest Routes
MCTS	100	2725.06	3.40	9.39
Distance-MCTS	100	2432.60	3.31	10.87
Cluster-MCTS	100	258.19	4.12	15.76
Retro*-0	100	1706.05	3.30	9.75
Cluster-Retro*-0	100	1654.43	4.85	16.59

Table S4 Building block average statistics for different search algorithms on the ChEMBL100 dataset.

Algorithm	Coverage (%)	Unique Rate (%)	Unavailable BBs (%)	Avg. Solvable Routes (%)	Post-Filtering Solved Molecules (%)	Experiment 2 Solved Molecules (%)
MCTS	56.94	13.41	36.22	1.36	49.00	71.00
Distance-MCTS	53.02	11.34	37.02	1.49	49.00	70.00
Cluster-MCTS	17.85	2.34	47.47	0.64	17.00	49.00
Retro*-0	39.19	8.74	39.79	1.37	47.00	93.00
Cluster-Retro*-0	31.40	13.07	40.39	0.28	11.00	57.00

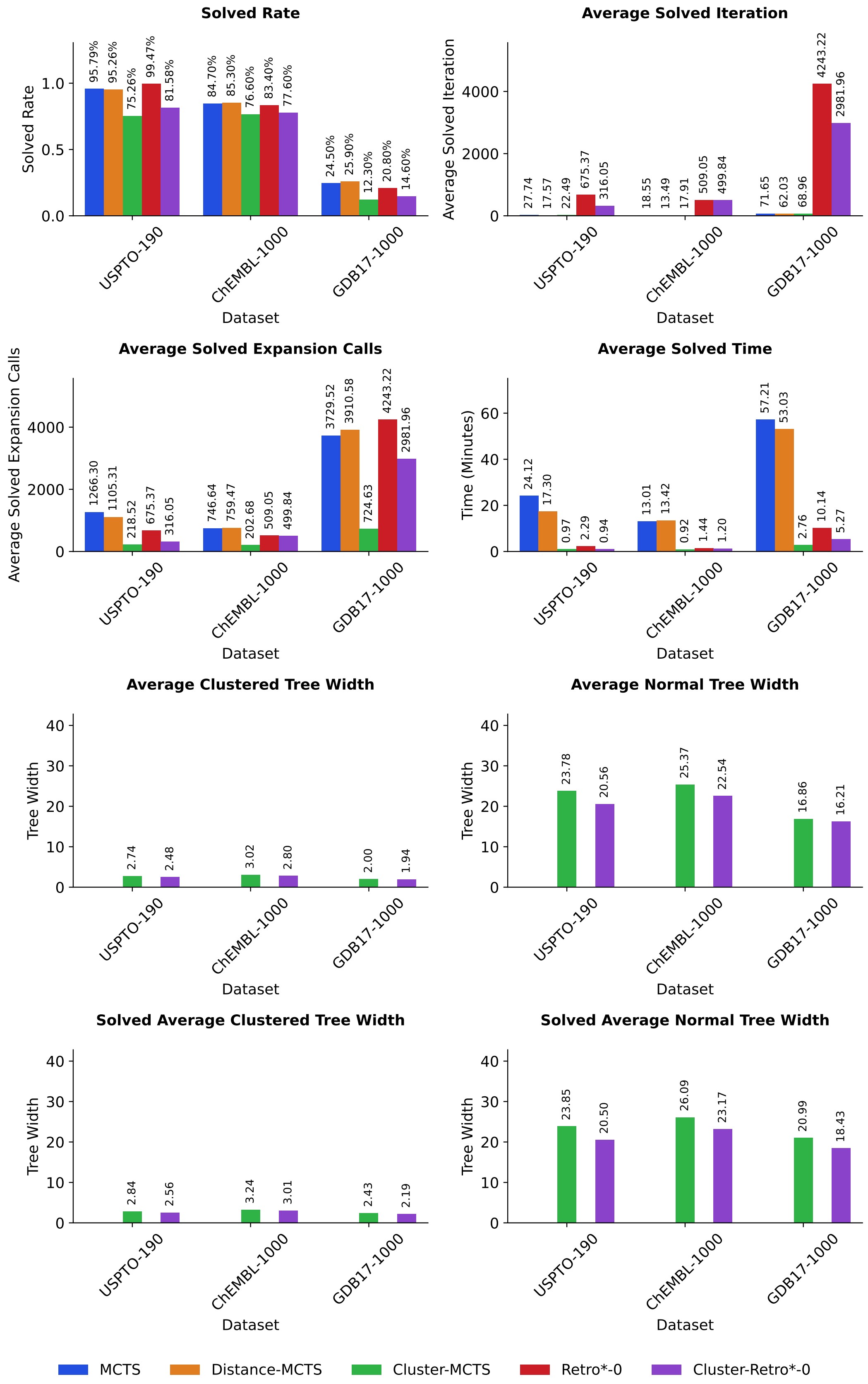


Fig. S1 Summary statistics for synthesis planning with different search algorithms using the eMolecules building blocks, highlighting average statistics for solved rates, algorithm iterations, single-step model expansion calls, and success time. Furthermore, the expansion model reactions that were added to the search tree, with and without clustering, for all and only solved molecules.

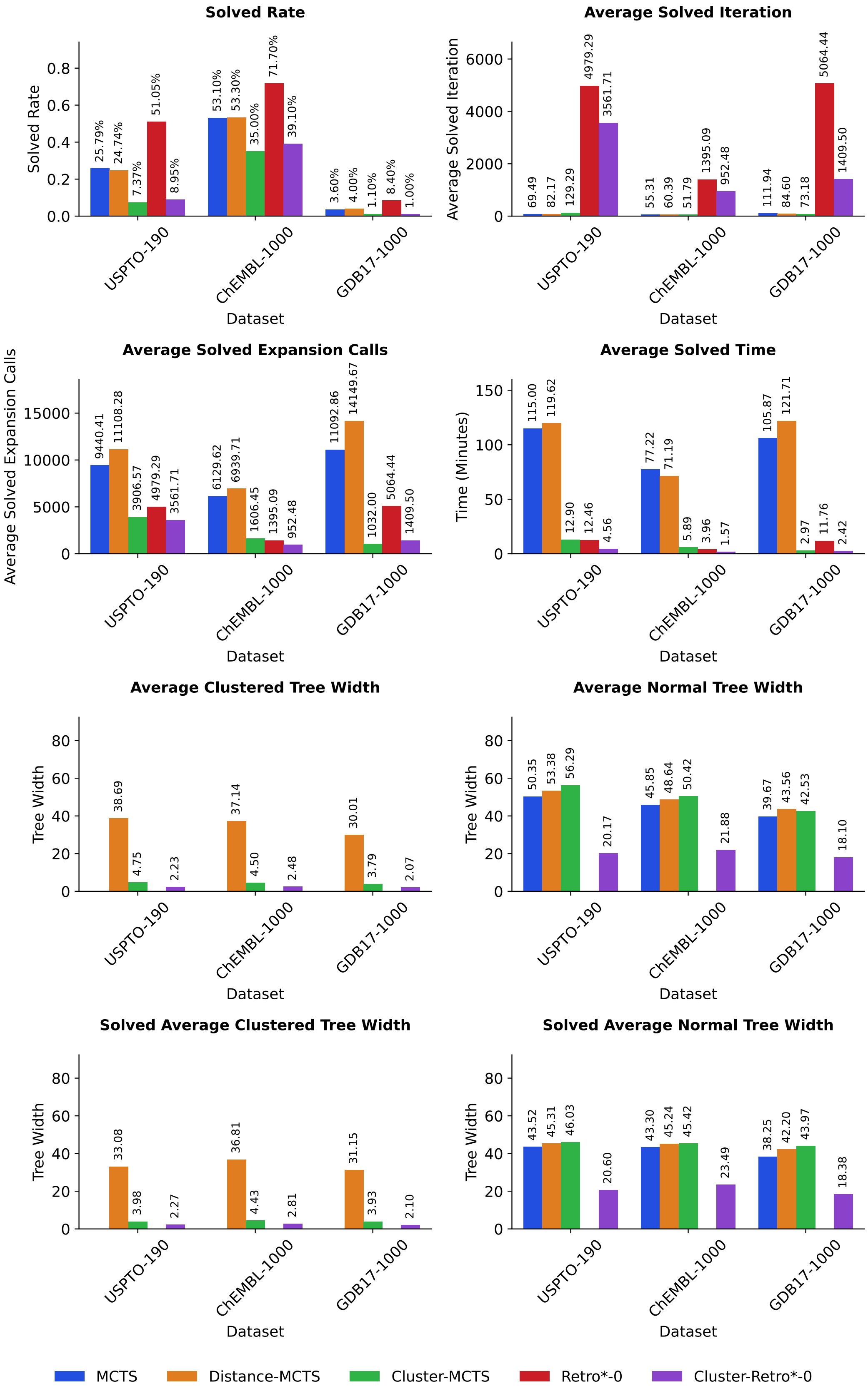
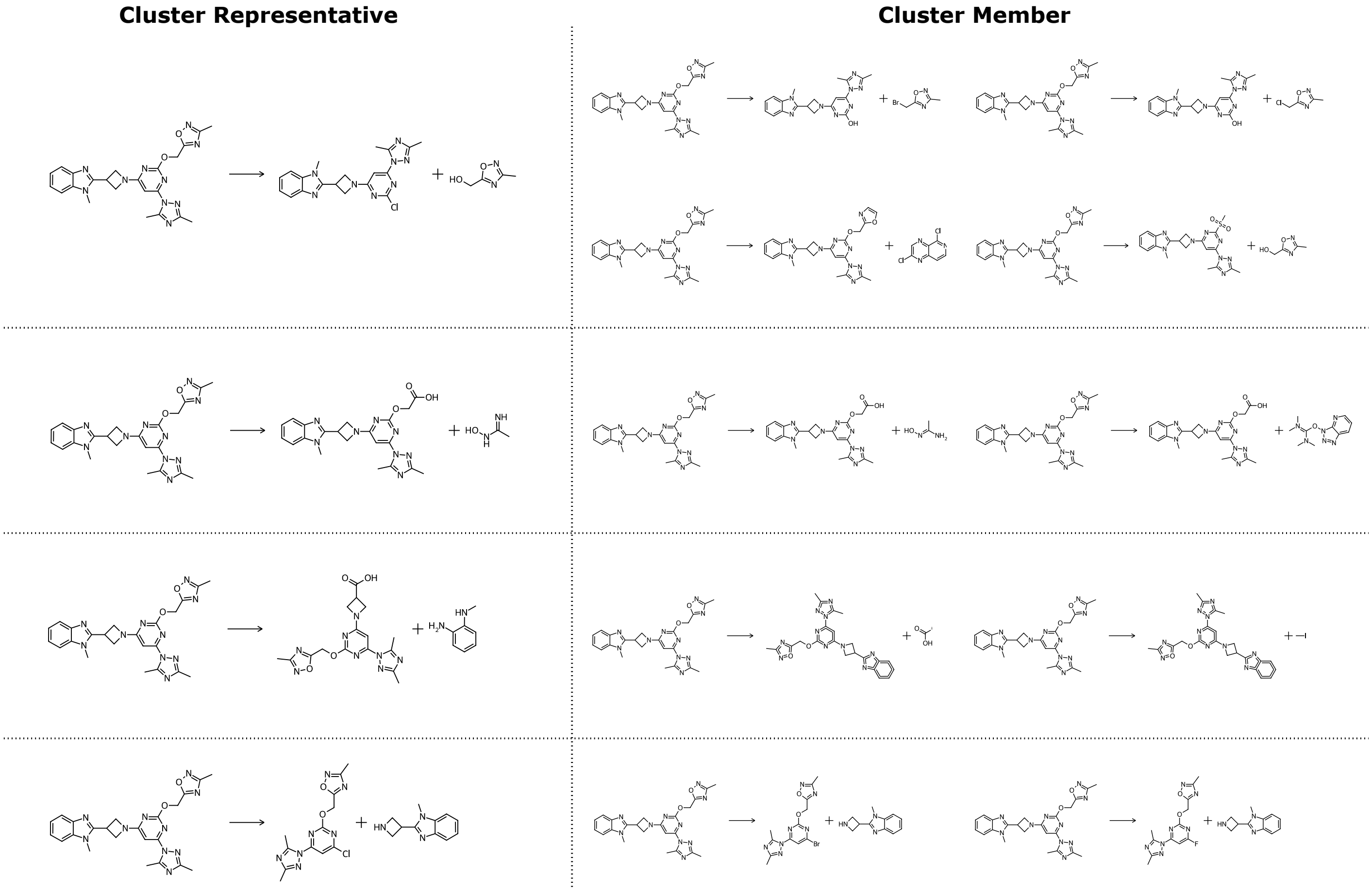


Fig. S2 Summary statistics for synthesis planning with different search algorithms using the eMolecules building block set, excluding building blocks used in routes found by prior best-first Retro*-0 search.



Cluster Representative

Cluster Member

Fig. S3 Single-Step Model Clustering Example. Highlighted are the important disconnections identified by reaction clustering and their ignored cluster members. Non-sanitizable reactants are included for exemplary visualization purposes.

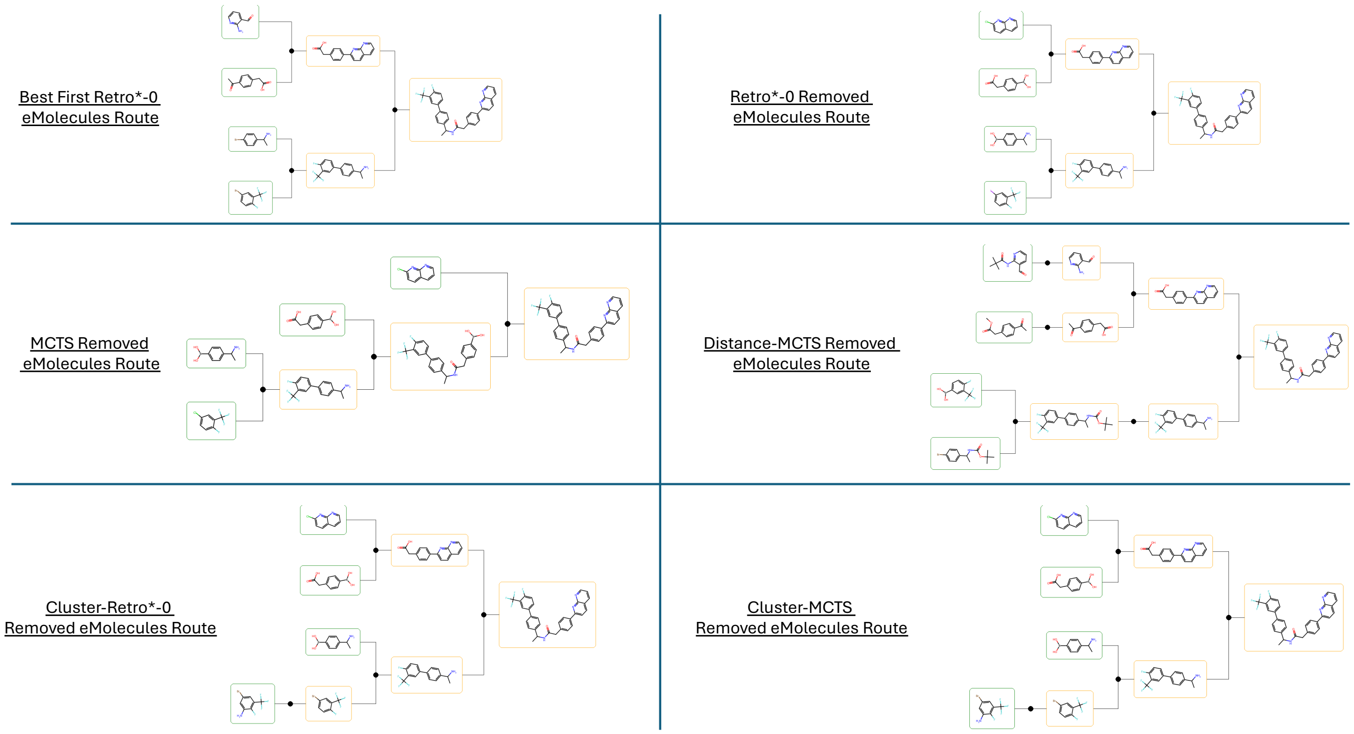


Fig. S4 Comparison of routes obtained using a Retro*-0 approach with all available eMolecule building blocks against evaluated algorithms that do not have access to the best-first building blocks.

Case Study: Product A and B from Zipoli et al.

Table S5 Comparison of search results for Products A and B[31] across different algorithms. The table reports the ability to find a synthesis route, the minimum number of reaction steps in the shortest route found, the count of overall unique routes and also routes with unique building blocks, the minimum number of unique building blocks in a single route, and the total number of unique building blocks identified across all routes.

Product	**Algorithm**	Success	Min. Number Reactions	Unique Routes	Unique BB Routes	Min Unique BBs in Route	Total Unique BBs
A	MCTS	True	3	1976	1181	4.0	180
A	Distance-MCTS	True	3	2737	1301	4.0	231
A	Cluster-MCTS	True	5	659	466	4.0	115
A	Retro*-0	True	4	836	758	4.0	121
A	Cluster-Retro*-0	True	6	1042	620	5.0	215
B	MCTS	True	5	2	2	5.0	12
B	Distance-MCTS	True	5	16	14	4.0	19
B	Cluster-MCTS	True	7	3	3	5.0	11
B	Retro*-0	True	5	11	11	5.0	19
B	Cluster-Retro*-0	False	-	-	-	-	-

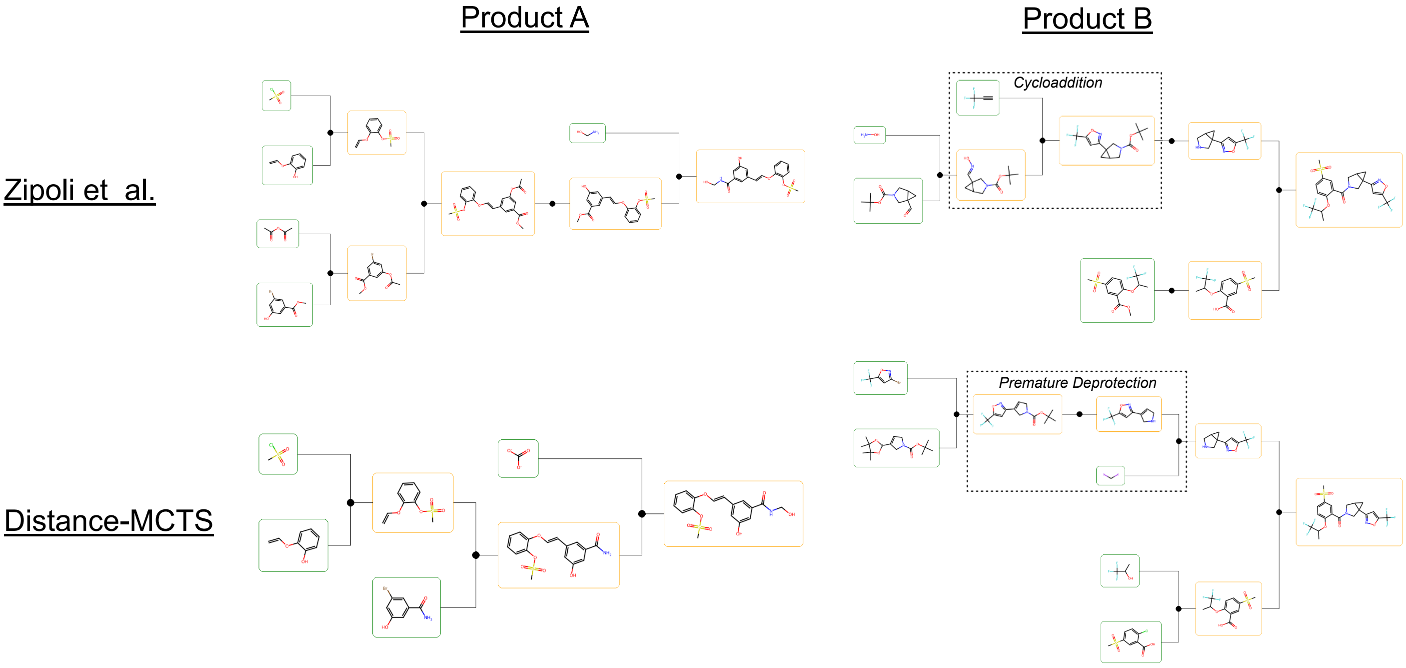


Fig. S5 Evaluation of diversity search synthesis routes for case-study Products A and B compared to literature-guided retrosynthesis[31]. For Product A, Distance-MCTS identified a route that conceptually matches the reported reaction steps but utilizes different building blocks. This modification eliminates a protection step, resulting in a pathway that is one step shorter. The route identified for Product B corresponds to a slightly longer, non-literature-guided synthesis route containing a premature deprotection step. Notably, the search did not recover the [3+2] cycloaddition route found by literature-guidance[31]. Since the required building blocks were present in the set, this failure suggests that the template-based single-step model failed to predict the specific disconnection.

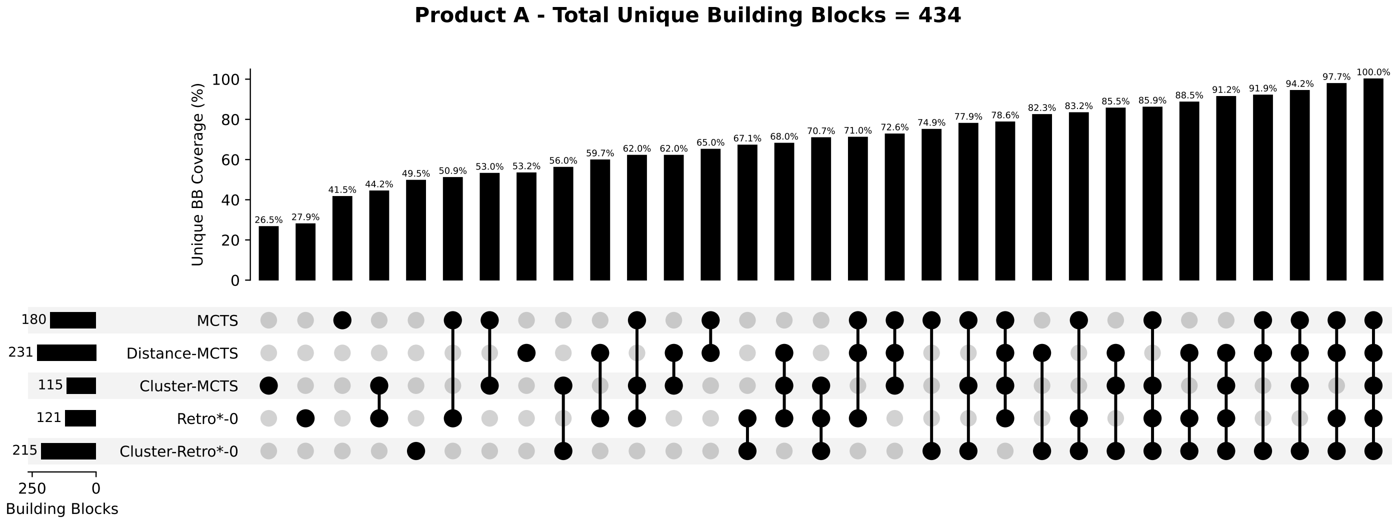


Fig. S6 Building block set intersection for Product A[31]. This UpSet plot visualizes the overlap between the unique building blocks discovered by each search algorithm. The matrix of connected dots shows the algorithms contributing to each combination, while the horizontal bars on the left quantify the total number of unique building blocks contributed by each algorithm. The vertical bars at the top display the union coverage rate for each combination: the percentage of all 434 unique building blocks (from all algorithms combined) covered by the union of selected algorithms.

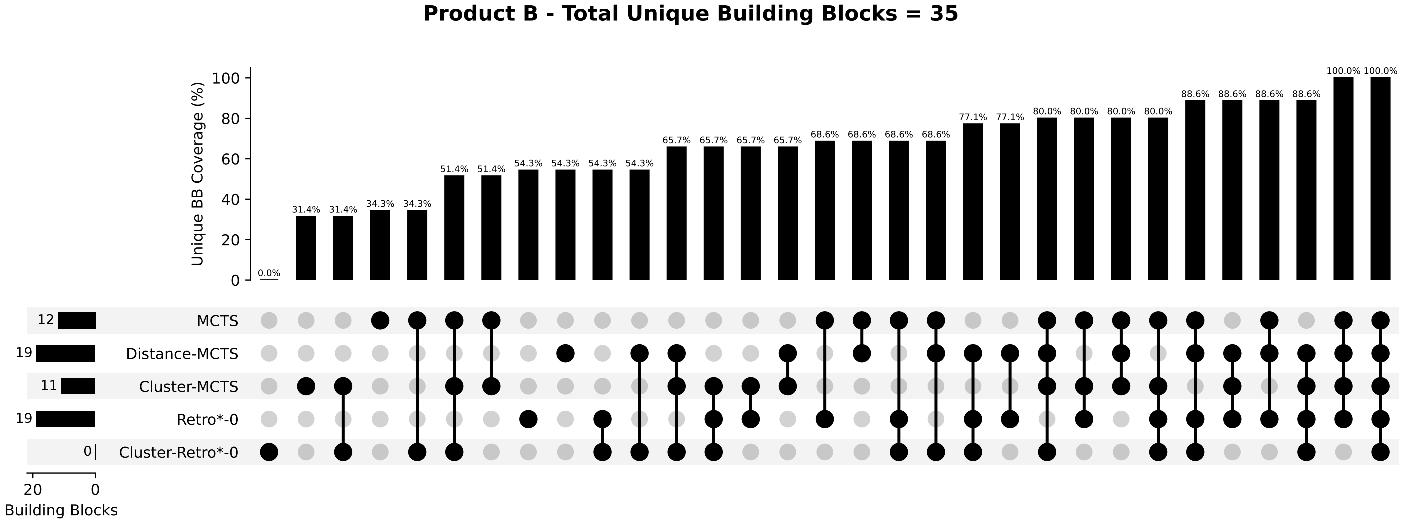


Fig. S7 Building block set intersection for Product B[31]. This UpSet plot visualizes the overlap between the unique building blocks discovered by each search algorithm. The matrix of connected dots shows the algorithms contributing to each combination, while the horizontal bars on the left quantify the total number of unique building blocks contributed by each algorithm. The vertical bars at the top display the union coverage rate for each combination: the percentage of all 35 unique building blocks (from all algorithms combined) covered by the union of selected algorithms.