ML-driven pathway design and validation in automated synthesis

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Automation gap in chemical synthesis

Advances in laboratory automation promise to decrease the manual effort of synthesis, but determining *how* to synthesize a compound still requires expert chemist knowledge

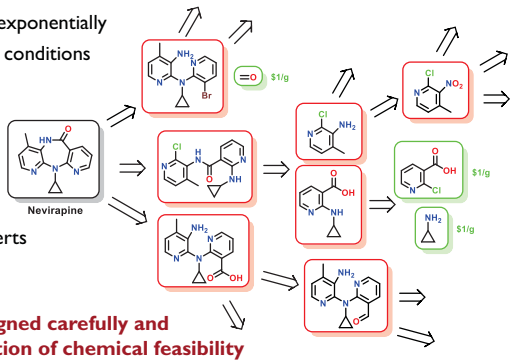
Hwang® and Coley® et al., *Chem. Comm.* **2017**

Godfrey, Masquelin, and Hemmerle, *Drug Discov. Today* **2013**

Computer-aided synthesis planning (CASP)

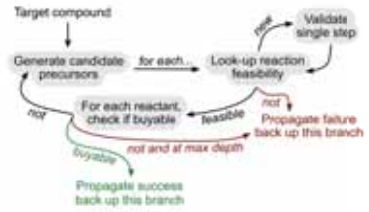
Pathways can be generated through recursive *retrosynthetic* expansion, but…

- The search space grows exponentially
- Suggestions must include conditions in addition to structures
- Disconnection rules are imperfect and may not be chemically feasible
- Detecting and reducing these false positives is challenging, even for experts
- No system has achieved wide-spread adoption



Pathways must be designed carefully and with explicit consideration of chemical feasibility

Extensible framework for pathway design



Key elements include:

- Candidate precursor generation with awareness of chirality
- Reaction condition recommendations
- Feasibility assessment through explicit prediction of reaction outcomes

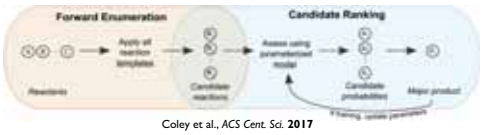
Coley et al., *Acc. Chem. Res.* **2018**

Validating via prediction of reaction outcomes

Retrosynthetic suggestions can be evaluated by solving the reverse problem:

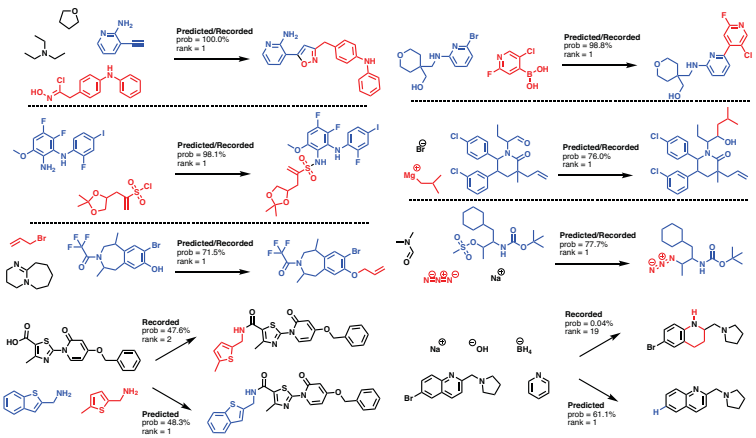
Given a set of reactants (and conditions), what is the major product?

[v1] Template-based, hybrid method



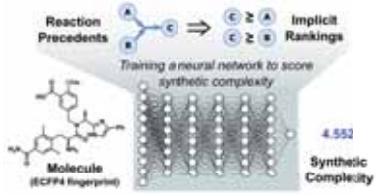
Coley et al., *ACS Cent. Sci.* **2017**

- Reaction templates define scope of possible outcomes
- Neural network model ranks candidates



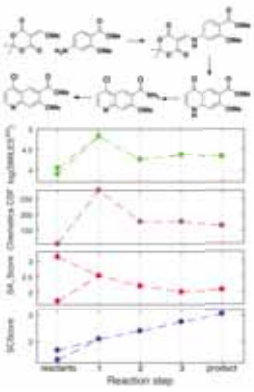
Guiding a retrosynthetic search: SCScore

To overcome combinatorial explosion, the search is focused along promising directions likely to lead back to purchasable compounds



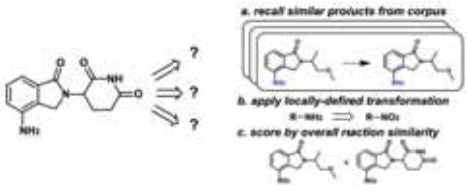
Published reaction data can be used to learn a synthetic complexity score to quantify if progress is being made in a synthetic step

Coley et al., *J. Chem. Inf. Model.* **2018**



Making focused retrosynthetic suggestions

An automated procedure can codify the workflow a beginner chemist might undertake when synthesizing a novel molecule: *look for similar compounds*



Model	top-n accuracy (%), n = 1	3	5	10	20	50
Liu et al. baseline	35.4	52.3	59.1	65.1	68.6	69.5
Liu et al. augmented	37.4	52.4	57.0	61.7	65.9	70.7
Similarity (this work)	**52.9**	**73.8**	**81.2**	**88.1**	**91.8**	**92.9**

- Disconnections proposed based on analogy
- Rare transforms need not be excluded
- Extends to multi-step planning
- Outperforms previous neural translation study

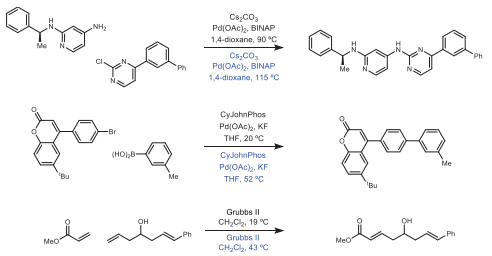
Coley et al., *ACS Cent. Sci.* **2017**

Recommending reaction conditions

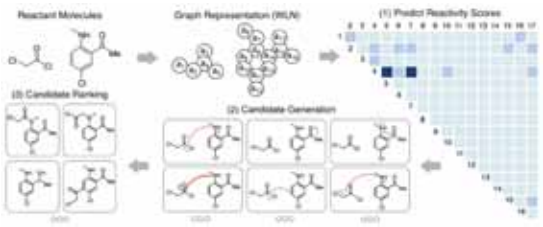
A recommender system suggests conditions for novel reactions

- Compatibility implicitly considered
- Close agreement to literature on test set

Gao, Struble, Coley et al., *submitted*



[v2] Template-free, fully-learned method



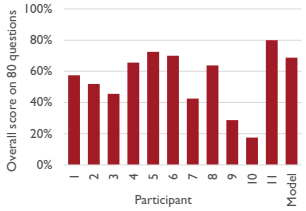
Jin, Coley et al., *NIPS* **2017**

- Template-free method overcomes bottleneck of template application
- Achieves higher accuracy and expert-level performance

USPTO-15K				
Method	Cov.	P@1	P@3	P@5
Coley et al.	100.0	72.1	86.6	90.7
WLN	90.1	74.9	84.6	86.3
WLDN	90.1	**76.7**	**85.6**	**86.8**
USPTO				
Method	|θ|	P@1	P@3	P@5
WLDN	3.2M	**79.6**	**87.7**	**89.2**
WLDN (*)	3.2M	83.9	93.2	95.2

Quantitative performance. Prediction at ranks 1, 3, 5. (*) denotes that the true product was added if not covered during previous stage

Human benchmarking



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