Exploring Chemical Space

Two (still immature) ways of traversing in the molecule space

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Chemical space in numbers

- New innovative molecules are needed for drug discovery.
- Only 12267 approved drugs[1]
- How big is the chemical space? 10^{60} drug like molecules[4]
- Huge untapped potential

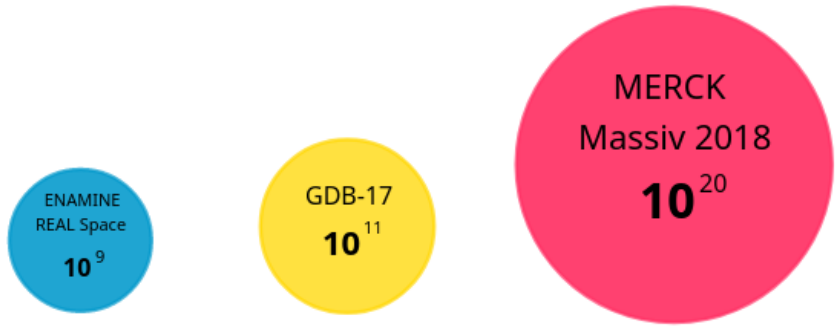


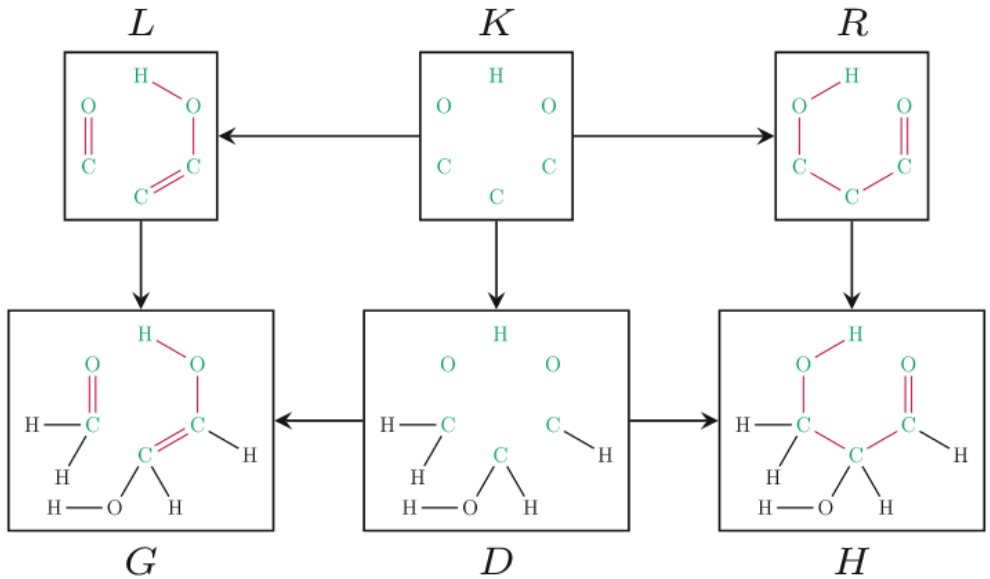
Figure: Chemical Space in Numbers.[2]

[1] on DrugBank 11.02.23

[2] Hoffmann, Torsten. The next level in chemical space navigation: Going far beyond enumerable compound libraries. Drug Discovery Today, 24(5):1148–1156, 2019

A rule based approach

- Using MØD as the underlying framework [1]
- Category theory embedded subgraph matching on molecule graphs
- A restriction on actual chemistry produces synthesizable molecules [5]
- Curated collection of 54 organic reactions by Hartenfeller et al.[3]

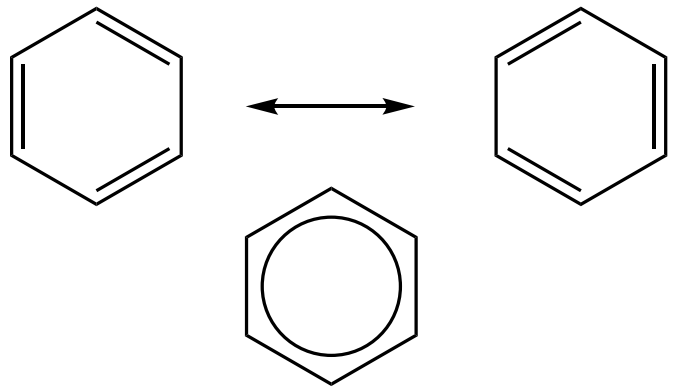


Term-Rewriting

- Chemical context needs to be explicity defined
- `ConstrainLabelAny` gives a lot of flexibility
- A liberal definition should be the sweet spot
- Much Needed: Negative Lists and Subgraph Matches

```
(...)
node [ id 1 label "_U" ]
edge [ source u target v label "_A"]
constrainLabelAny [
    label "Meso(_A,_B,_C,_D,_E,_F)"
    labels [label "Meso(-,=,-,=,-,=)" label "Meso(=,-,=,-,=,-)"]
    ]
constrainLabelAny [
    label "Halo(_U)"
    labels [label "Halo(Cl)" label "Halo(Br)" label "Halo(I)"]
    ]
]
```

Term-Rewriting



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7       ]
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11      ]
12  ]
```

Term-Rewriting

- Chemical context needs to be explicity defined
- `ConstrainLabelAny` gives a lot of flexibility
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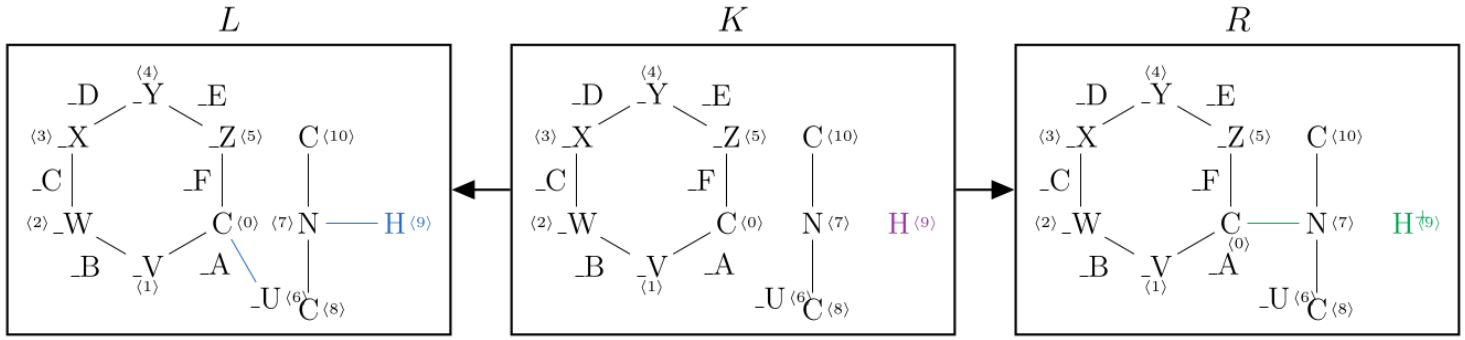
- Much Needed: Negative Lists and Subgraph-Terms

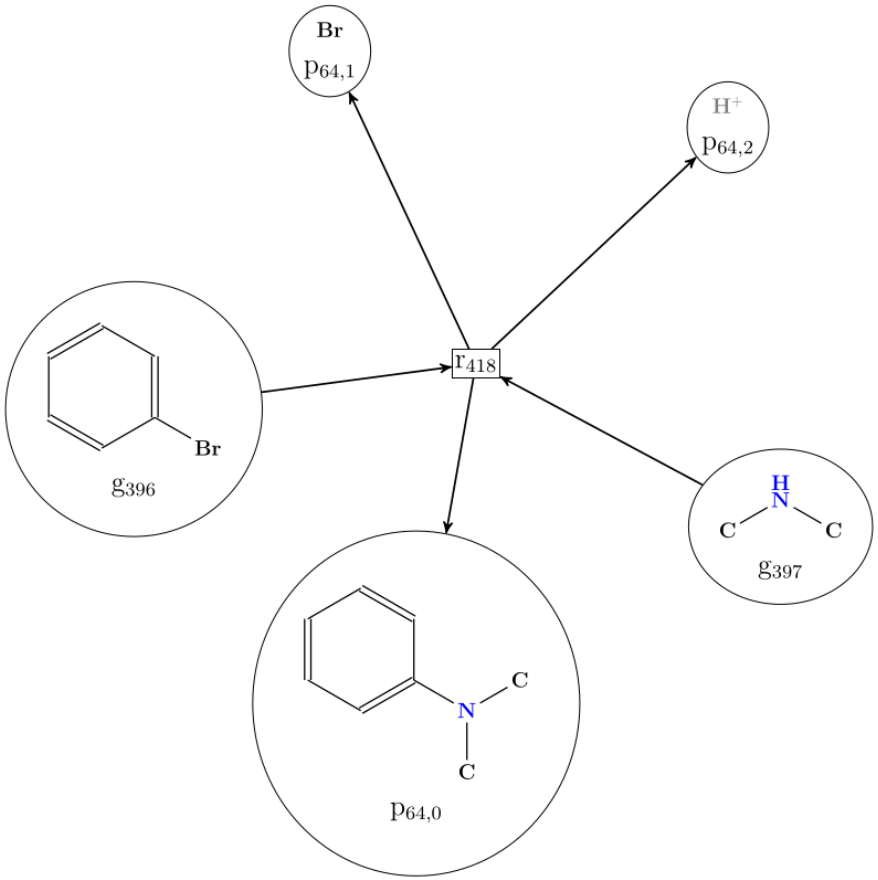
65.1.1 Buchwald-Hartwig-amine



Files: out/819_r_418_10300010_{L, K, R}

`Permut(_V,_W,_X,_Y,_Z)` ∈ {'`Permut(C,C,C,C,C)`', '`Permut(N,C,C,C,C)`', '`Permut(C,C,C,C,N)`'
`Meso(_A,_B,_C,_D,_E,_F)` ∈ {'`Meso(-,=,-,=,-,=)`', '`Meso(=,-,=,-,=,-)`'}
`Halo(_U)` ∈ {'`Halo(Cl)`', '`Halo(Br)`', '`Halo(I)`'}

Term-Rewriting



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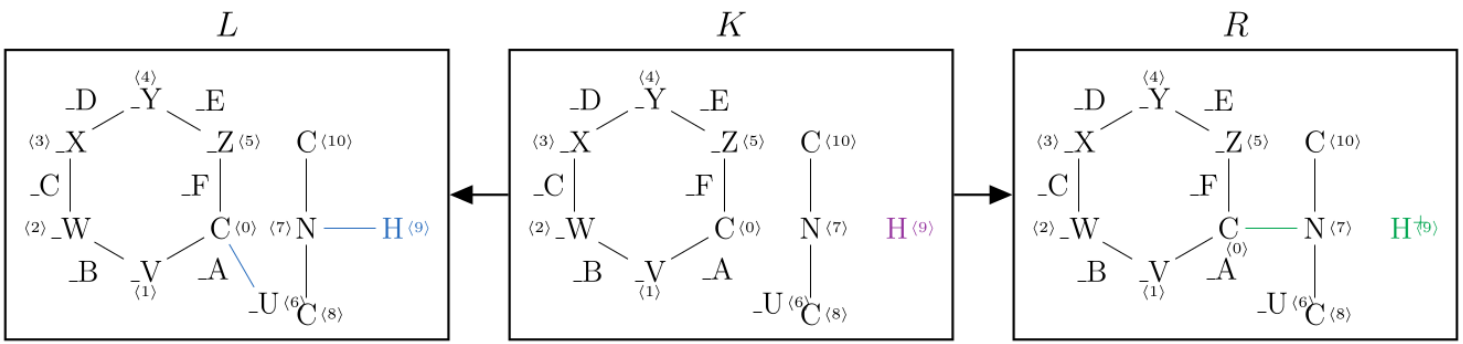
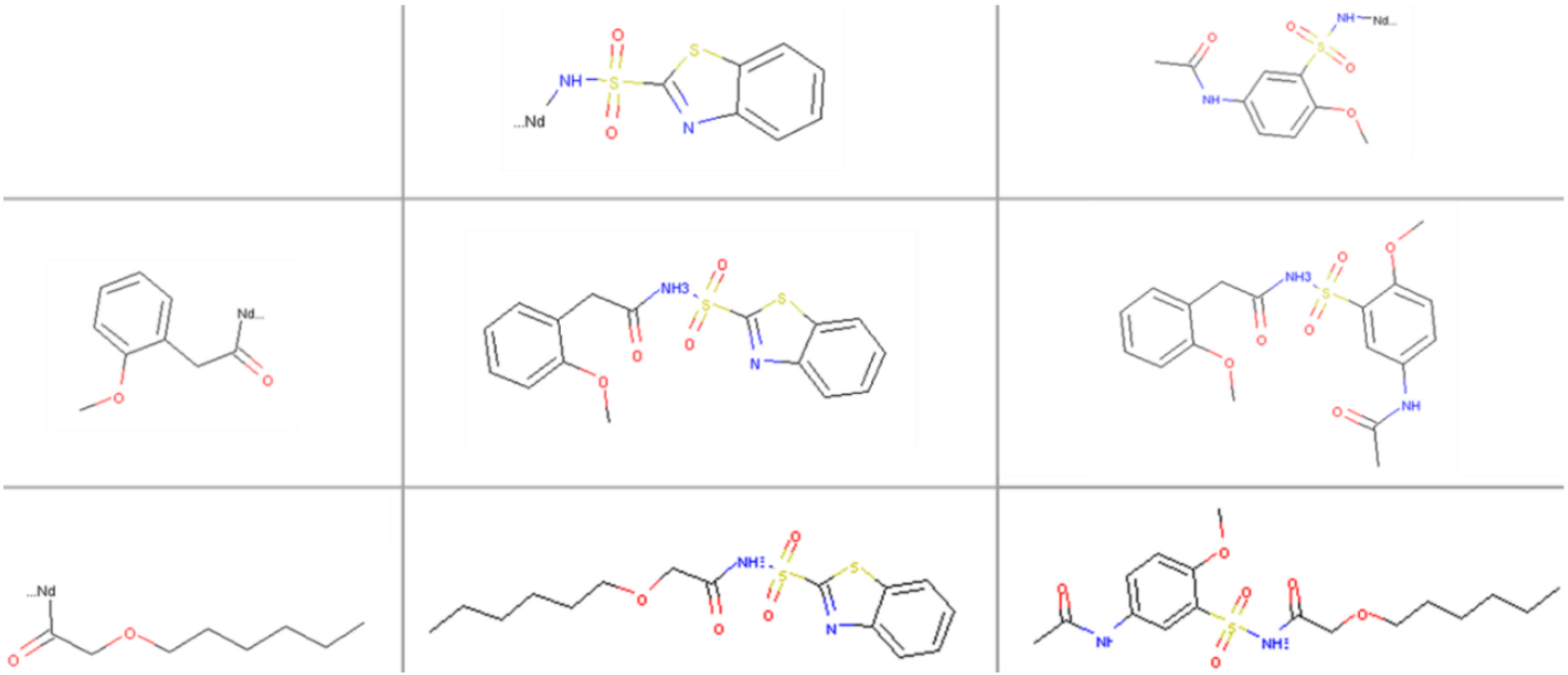


Files: out/819_r_418_10300010_{L, K, R}

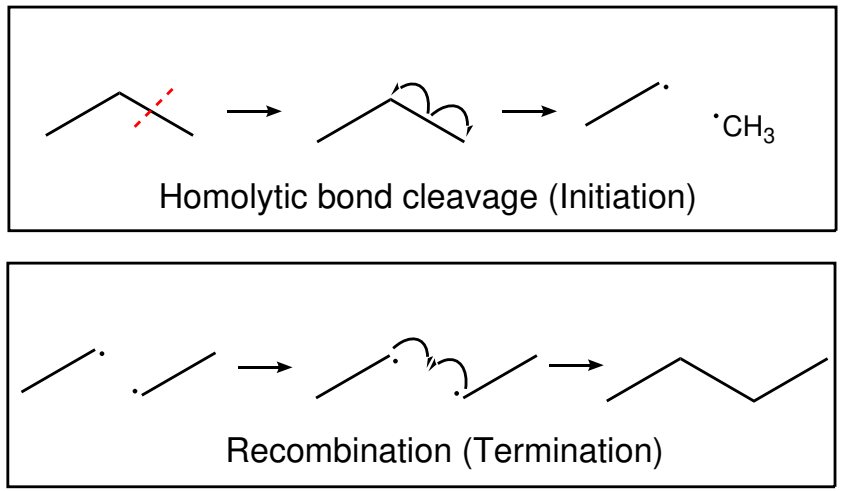
A rule based approach

- A first test is *planned* using the ENAMINE synthesize-on-demand library



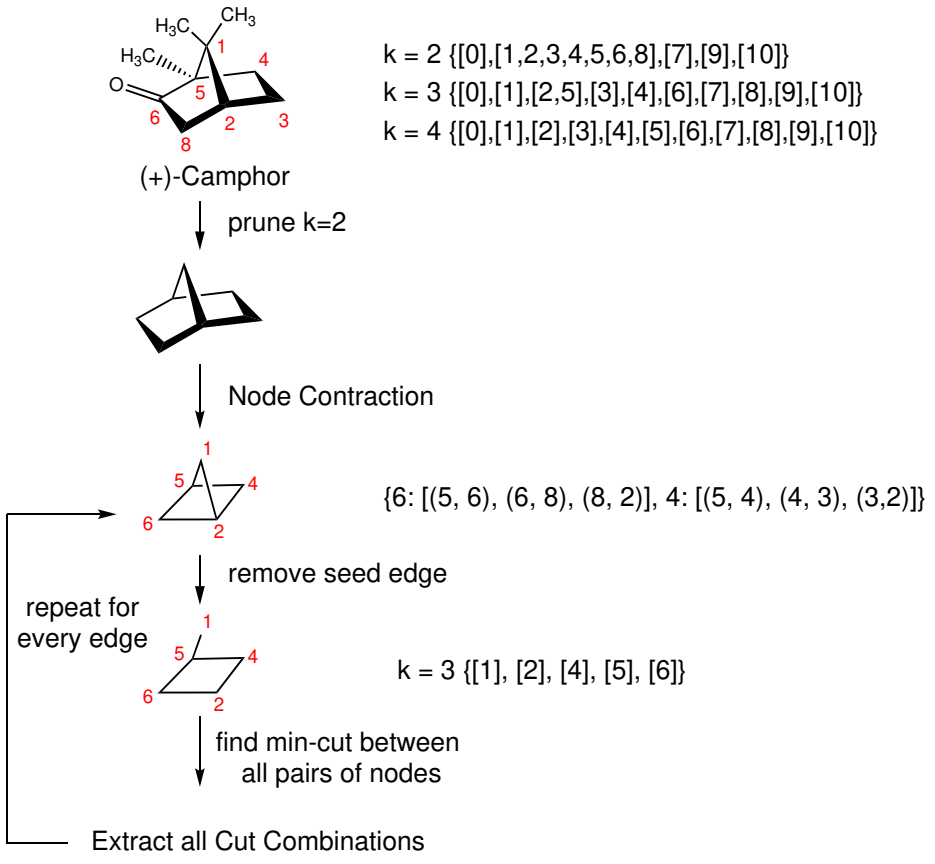
Crossover mutations

- Two parent molecules each cut into two fragments
- Corresponds to the formation of radicals in chemistry
- No restriction by relying on reactions
- exhaustive graph bipartitioning



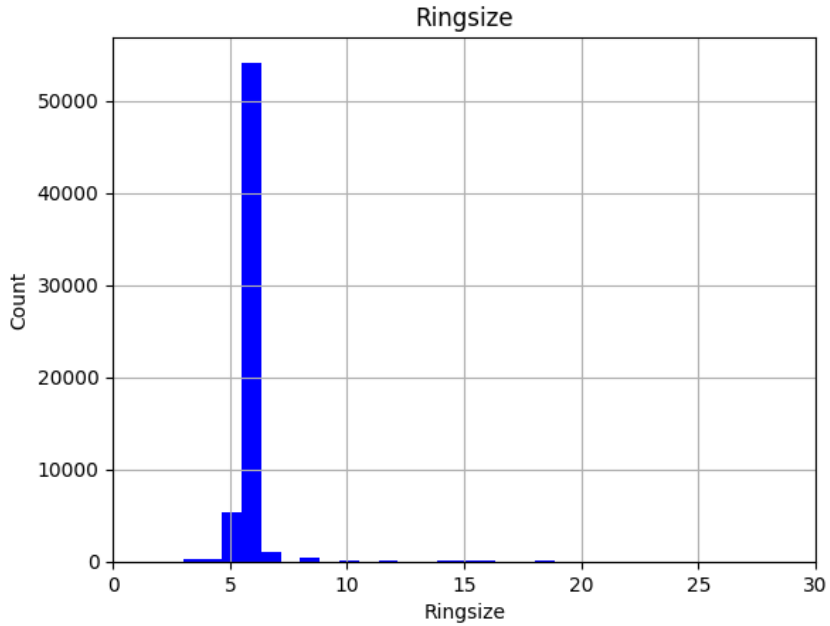
Generating all possible cuts

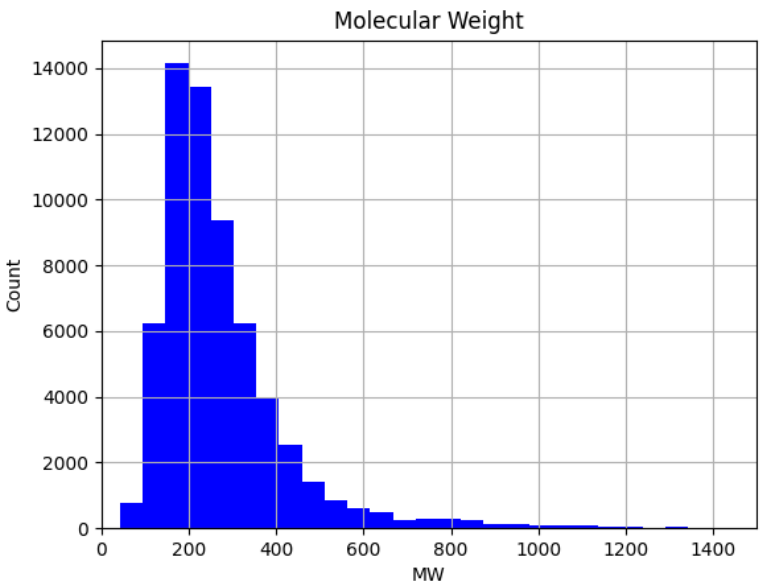
- k-connected-components for k = 2,3,4 [6]
- remove sidechains (k=2)
- contract nodes
- remove random seed-edge of graph
- check k-connected-components after removal
- get minimum-cut of every pair of atoms in these connected components

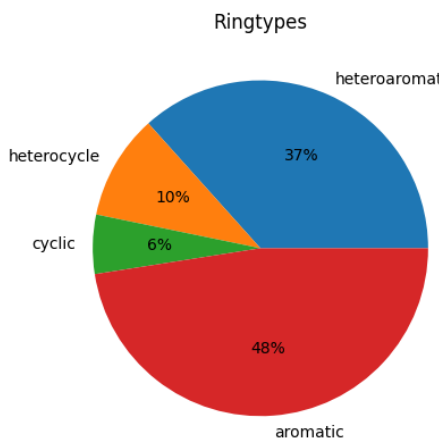


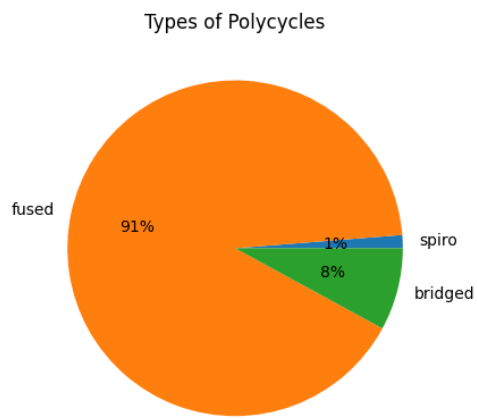
A superficial look at Sigma Aldrich catalog

- Atleast 1 Ring,
  1 Carbon-Atom,
  no disconnected
  components
- 117k $\rightarrow$ 62k compounds
- High diversity



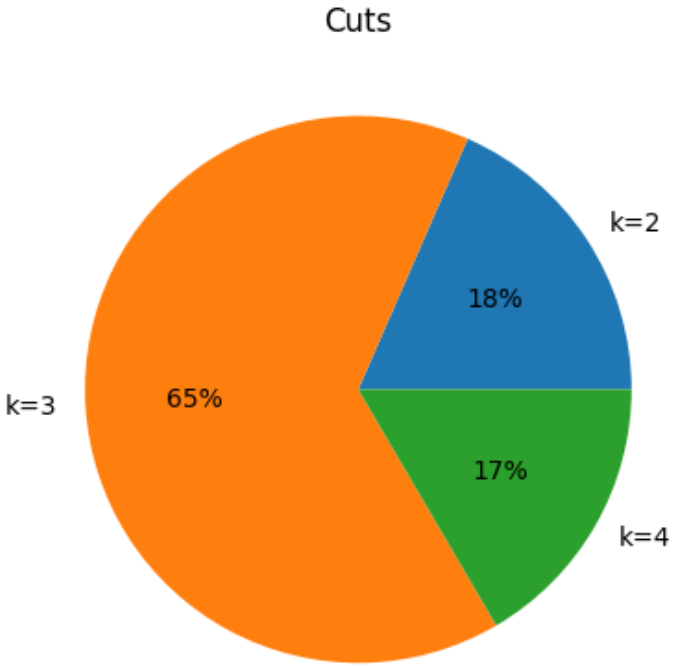


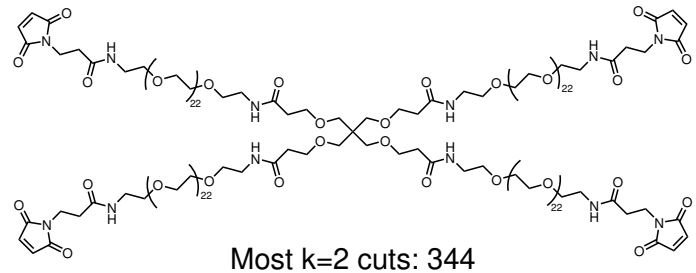




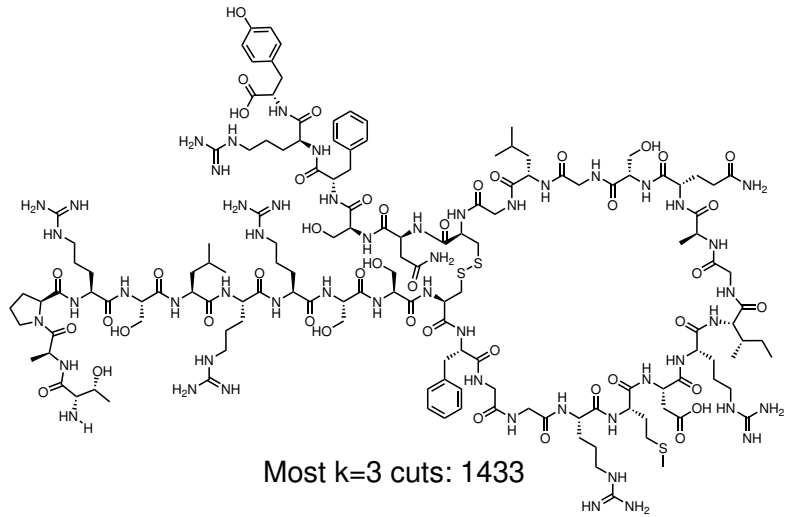
A superficial look at Sigma Aldrich catalog

- Found 3.1 M cut combinations

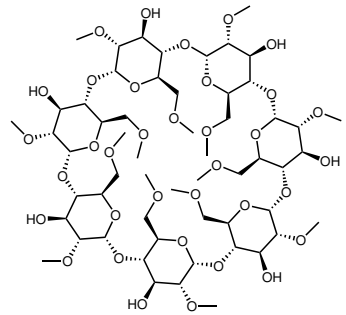




Most k=2 cuts: 344



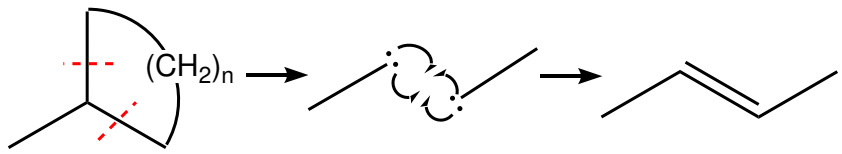
Most k=3 cuts: 1433



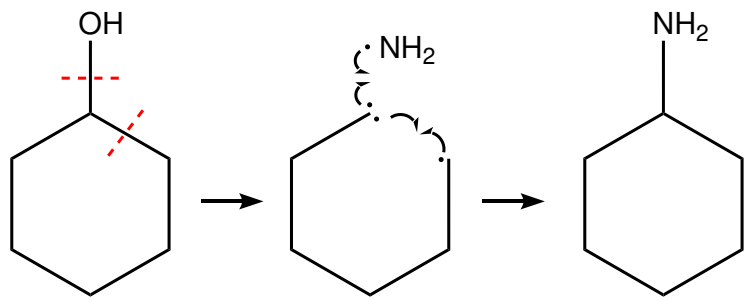
Most k=4 cuts: 630

Open Questions of the fragment recombination

- Allow Termination of multiple radicals at the same atoms?
- How to proceed with fragments having a missmatched number of radicals?
- Allow Recombination to previous bond pattern?
- Matching of single-node-fragments?
- Essentially point mutations, takes a lot of space ($\sim$ 32%) in the cut space



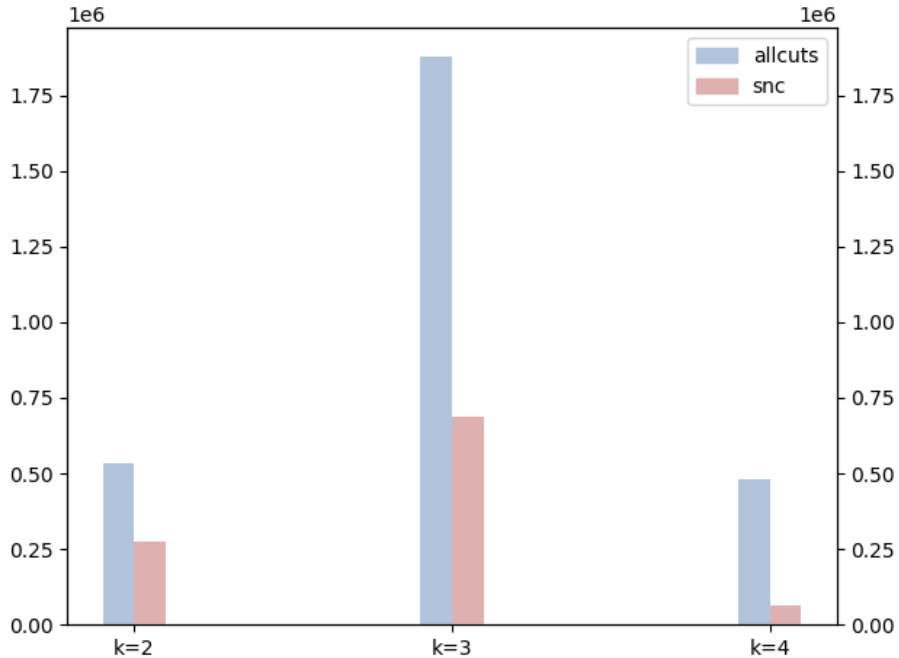
Changing of bondorder



Recombination into "old" bonds

Open Questions of the fragment recombination

- Allow Termination of multiple radicals at the same atoms?
- Matching of single-node-fragments?
- How to proceed with fragments having a missmatched number of radicals?
- Allow Recombination to previous bond pattern?
- A lot of point mutations, taking lot of space ($\sim$ 32%) in the cut space



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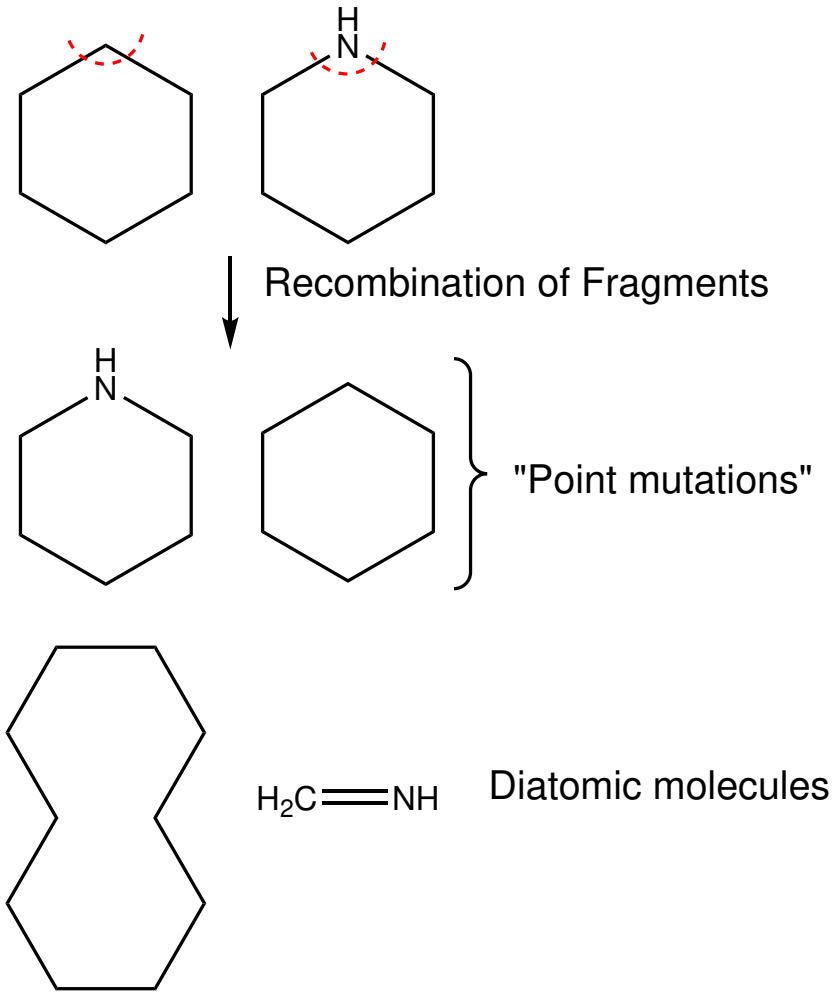

How to ensure chemical meaningfulness?

- Possible Restrictions and filters:

- Remove unstable functional groups (violating Erlenmeyer-Rule etc.)
- Account for ring strain (violating Bredts-Rule, etc.)
- Most lead compounds are in range $100 < \text{MW} < 350$ Da
- Empiric MedChem rules: Lipinski Ro5, Lily Medchem [2]

Thanks to my Supervisors Peter and xtof

Special Thanks to Bruno!

Thank You!

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