



Combinatorial Chemistry and Library Design using Pipeline Pilot

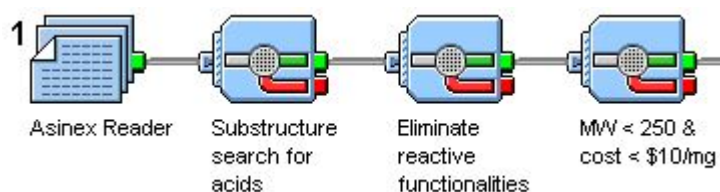
If you use combinatorial chemistry and library synthesis techniques as part of your lead generation and lead optimization process, there are several computational tasks that you can optimize and automate using Pipeline Pilot

1. Identification and selection of reagents
2. Definition and enumeration of virtual or real libraries
3. Library profiling and subset selection for diversity or similarity

These processes can form separate workflows, or can be automated as a seamless process. For end users chemists, the workflows can be deployed through a simple web interface such as Pipeline Pilot Pipeline Pilot Web Port, or one of your own design.

Reagent Selection

Pipeline Pilot can be used to automate the process of reading reagent data direct from vendor files, or from compendia such as MDL's ACD or Accelrys' CAP. It can be used to filter reagents for desirable or undesirable substructures (e.g. reactive substructures), without requiring that the reagents be loaded into a database. Many property calculations are available to focus on desirable reagents and custom filters can be implemented to select preferred vendors or apply availability and pricing criteria. Selected reagents can then be stored in a file or database, or can be passed directly into the enumeration components. If a core plus r-groups enumeration method will be used (see below) then Pipeline Pilot provides components to clip the reagents, which can be applied before storage.

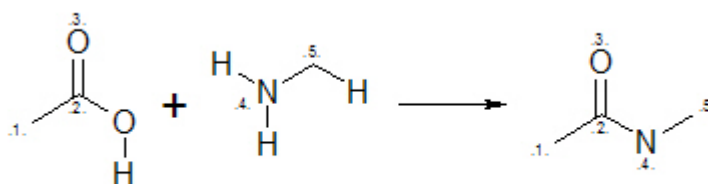


Library Enumeration

Enumeration of a library can be performed using reaction based, or core plus Rgroups (also known as Markush based) methods

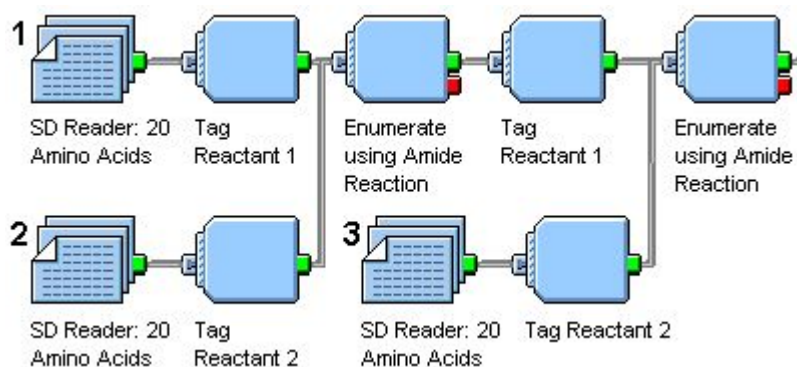
Reaction-based enumeration

A series of generic reactions are specified using MDL RXN format (which can be sketched in a variety of editors) or Daylight SMIRKS format.



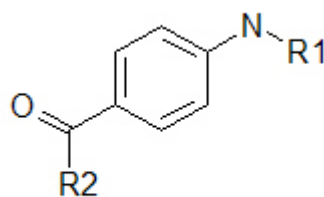
Generic reaction for amide formation

Each reaction, or set of reactions is loaded into a component, into which reagents are piped. The products of the reaction emerge from the pass port, and any reagents that cannot react from the fail port. The output may be saved to a file or database, displayed in a viewer, passed to a post processing step, or passed directly into another enumeration component to perform the next step in a synthesis scheme. The component provides extensive control over exception handling, for example for reagents with multiple mappings and associated components allow protection and deprotection steps to focus a reaction to the correct reaction site.



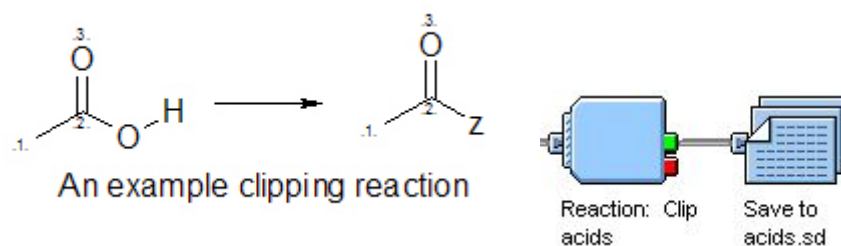
Core plus R-groups (Markush) Enumeration

To enumerate a library using a markush structure, the library scaffold must be provided with R groups marking the substituent positions.



Core definition

Reagents must be provided in clipped format. A component is available to perform the clipping using a transformation.

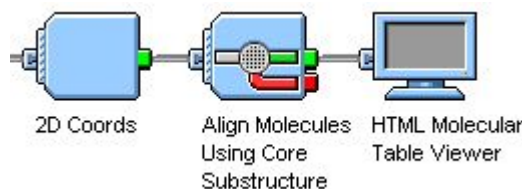


An example clipping reaction

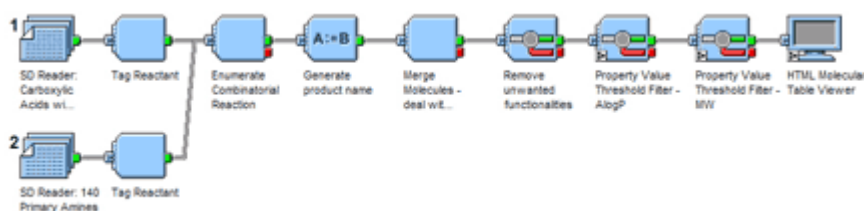
The core plus clipped reagents are then used by the enumeration component to produce the products. An unenumerated representation of the library may be saved as an MDL RG file, and existing RG files can be directly enumerated using an option in the RG reader.

Library Analysis and Subset Selection

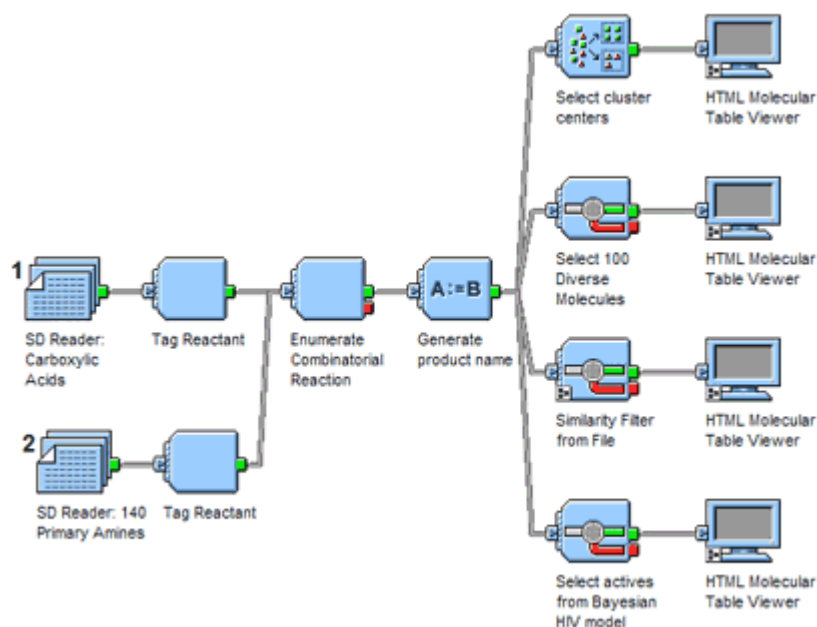
Once a set of structures has been enumerated a number of post processing steps can be applied using components from the Pipeline Pilot chemistry and modeling collections. The enumeration components provide initial coordinates for the products but further clean up can be applied using 2D coordinates generators, and products can be aligned using a substructure (e.g. the markush core) to orient all molecules in the same way for viewing.



Libraries can be rapidly profiled using Pipeline Pilot property calculators and library members with undesirable properties removed immediately



A number of subset selection methods may be applied. Diverse subsets may be selected according to a maxmin diversity metric, or by clustering the molecules and selecting a representative such as the centroid from each cluster. For lead optimization, similarity selection may be used to select near neighbors to know leads, or clustering may be used to select all library members clustering with a known active. A virtual screening model may even be applied directly to the enumeration output to select only those members predicted to be active



In all cases, the post processing may be applied directly to the output of the enumeration, without the need to store intermediate files of the entire library. In cases where very large virtual libraries are being enumerated, this makes the process very much quicker and more manageable.

Web Deployment

For end user chemists, Pipeline Pilot allows protocol based applications such as those shown above to be presented through a web interface that is intuitive and easy to use for the chemist, but still takes full advantage of the high-speed processing and automation to tasks that Pipeline Pilot provides. Pipeline Pilot Pipeline Pilot Web Port allows such deployment, or users may take advantage of the client side SDK's to develop their own interface. One example of such a development is shown below.

The screenshot shows a web interface titled "Select Reaction's Reagents". At the top, there are fields for "Virtual Library Name" (set to "Index-Subst") and "Number of Reagents" (set to "7"). There are buttons for "Load New Data", "Load New Meta", "Select Library", "Load Data", and "Select Reaction". Below this is a "Reaction Structure" section showing a chemical reaction: A-C(=O)-B + A-C(=O)-C >> A-C(=O)-D. Underneath is a "Multiple Mapping Options" dropdown menu set to "React Reagent".

The interface is divided into two sections for reagents:

- Reagent 1:** Includes a "Source ID File" section with instructions to upload a file or select a package. It features a "Browse" button and a "Number of Reagents to Use (0-9)" input field.
- Reagent 2:** Similar to Reagent 1, with its own "Source ID File" section, "Browse" button, and "Number of Reagents to Use (0-9)" input field.

At the bottom left, there is a "React" button.

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