Predicting Generation of Potential Mutagenic Impurities within Mirabilis using the Condition Approach

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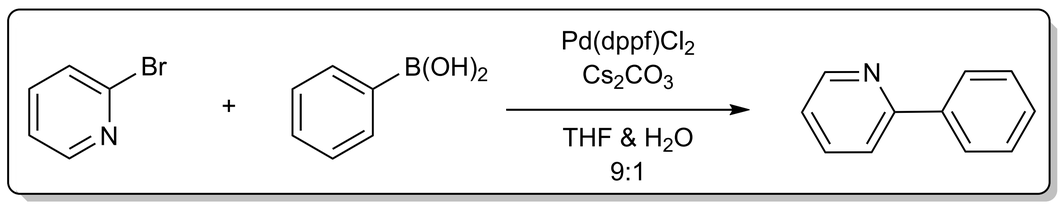
Performing a mutagenic impurity risk assessment requires evaluating the possible mutagenicity of all structures reasonably expected to be encountered in an active pharmaceutical ingredient (API) synthesis.[1] All potentially mutagenic impurities (PMIs) must be demonstrated to be suitably controlled by the process.[2] This can be done by analytical testing or through purge assessments, which represent a semi-quantitative means of assessing carryover without the need for significant analytical testing.

In the case of Valsartan, the potential formation of NDMA (following a change in the original manufacturing process) was missed and subsequently no assessment of control was performed.[3] Improvements to Mirabilis aim to facilitate the risk assessment process by utilising a new "condition approach". The approach allows implementation of "alerts" which will provide the user with a warning when a combination of intermediates and conditions may result in the formation of a PMI.

Mirabilis 3.0
Old Transformation Approach

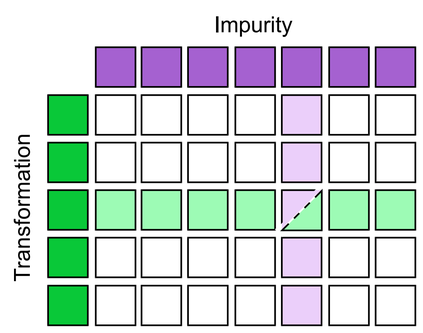
VS

Mirabilis 4.0
New Condition Approach

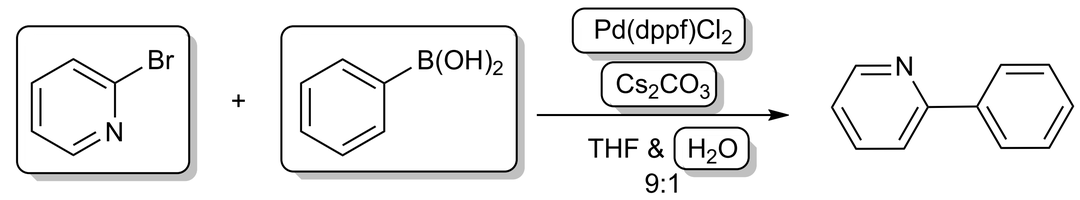


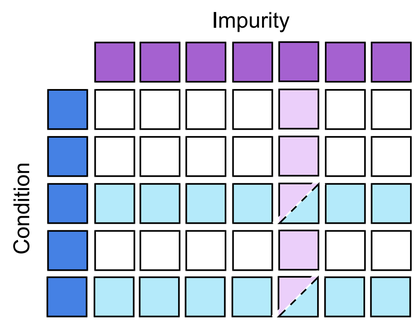
Scheme is identified as transformation based on bond changes at the reacting centre and likely associated reagents:

- Suzuki Coupling



Mirabilis will then find and return the expert derived purge factor for the impurity under the standard conditions of the identified transformation.[4]





Scheme is identified as a collection of independent functional groups and reagents (conditions):

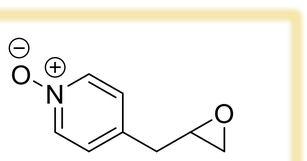
- Aryl Halide
- Boronic Acid
- Palladium Catalyst
- Weak Inorganic Base
- Water
- Pyridine-type Nitrogen
- Aryl C-H

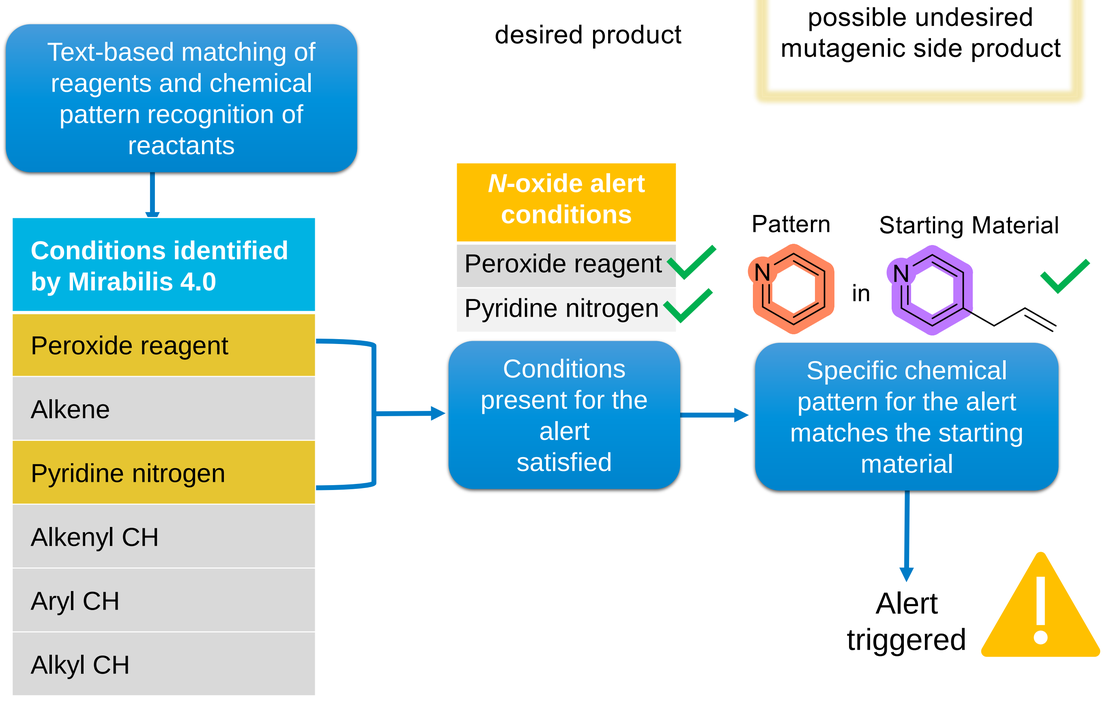
Mirabilis will then find and return the purge factors for the impurity in all the different conditions and the apply the highest value.

Condition approach and alerts

Just as the condition approach allows Mirabilis 4.0 to retrieve purge factor values based on the functional groups and reagents, it also allows the retrieval of 'alerts' for a reaction step, i.e., a note to the user that a mutagenic impurity may be formed either from the starting material or from unpurged impurities in previous steps.

- Logic is applied to retrieve the relative mechanisms and to exclude reactions that would be inhibited by competing conditions.
- For the following reaction (alkene oxidation to an epoxide), Mirabilis would alert the user to the potential undesired aromatic *N*-oxide PMI being formed.

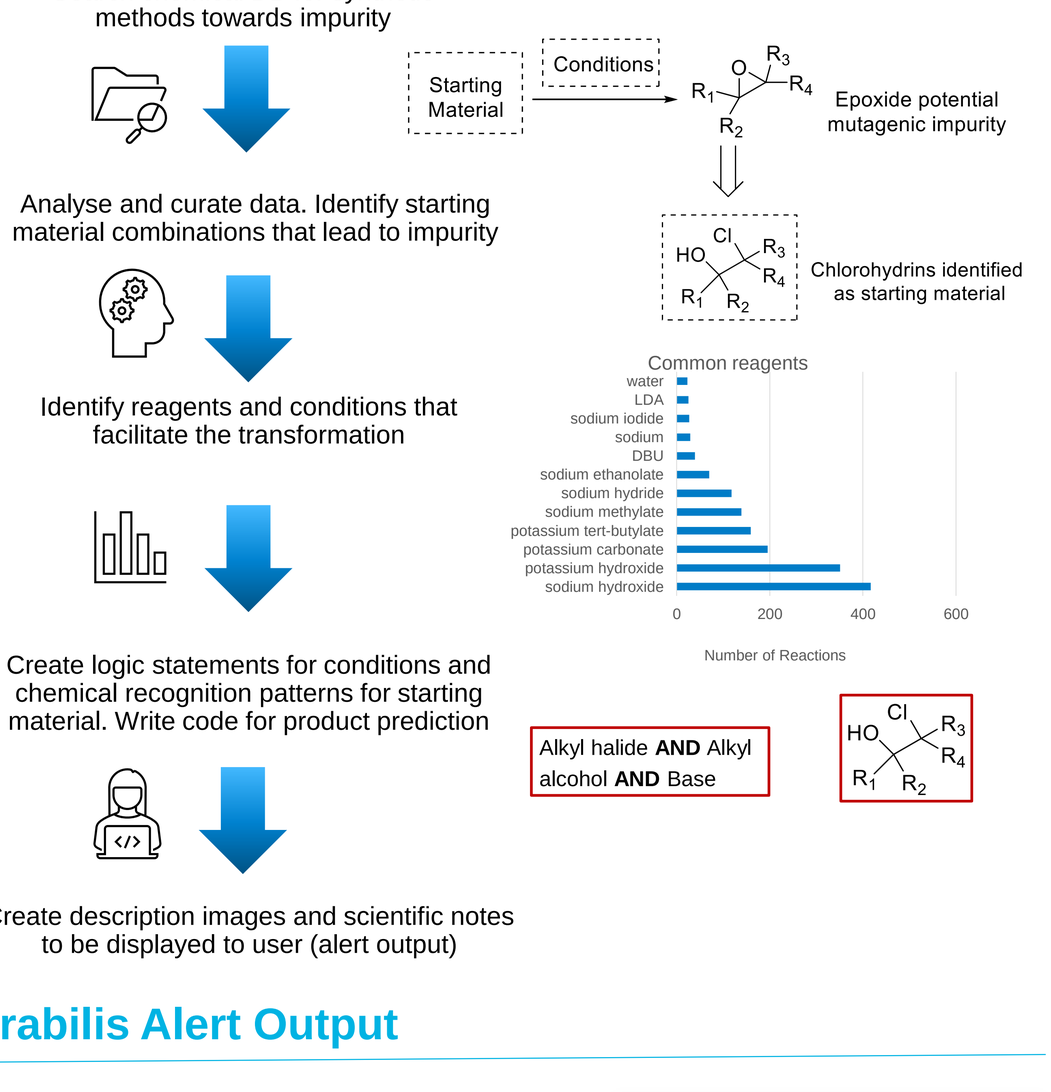




- The logic for the alert "Pyridine nitrogen AND Peroxide reagent" is fulfilled by the general conditions identified.
- The at-risk structure passes a specific pattern check
- The alert is triggered, and the user warned of potential PMI formation.

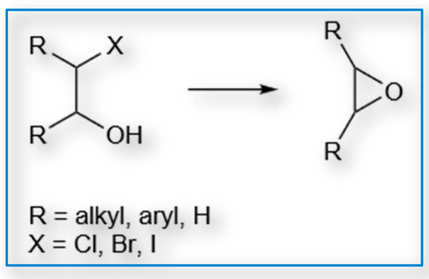
Researching and Creating Alerts

Halohydrins may lead to (mutagenic) epoxides under certain conditions. Below illustrates the process of identifying and writing an alert for epoxide formation in Mirabilis 4.0.



Mirabilis Alert Output

- The alert output contains a description picture along with scientific notes describing the conditions under which the mutagenic impurity is likely to form along with references.
- The transformation is then applied to the flagged structure and the structure of the possible impurity is predicted.



Conclusion

- The condition focus adopted for Mirabilis 4.0 allows reaction schemes to be broken down into their functional groups, reagents and conditions.
- This higher level of detail allows Mirabilis 4.0 to identify scenarios where a combination of starting material or products with certain reagents or conditions may lead to the synthesis of PMIs.
- 56 alerts have been researched and implemented into Mirabilis 4.0. Five impurities are covered thus far: *N*-nitroso compounds, aromatic *N*-oxides, haloalkenes, epoxides and primary alkyl halides.

References: **[1]** Conditions Potentially Leading to the Formation of Mutagenic Impurities, Mutagenic Impurities: Strategies for Identification and Control, 2nd Edition, Teasdale A, Wiley, 2022, 978-1-119-55121-8 **[2]** https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf **[3]** N-Nitrosamines, Mutagenic Impurities: Strategies for Identification and Control, 2nd Edition, Teasdale A, Wiley, 2022, 978-1-119-55121-8 **[4]** Burns MJ et al, Organic Process Research & Development, 2019, 23, 2470-2481

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