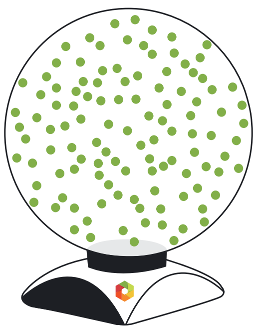
CATALYSIS CONSULTING

Combining DOE and PCA

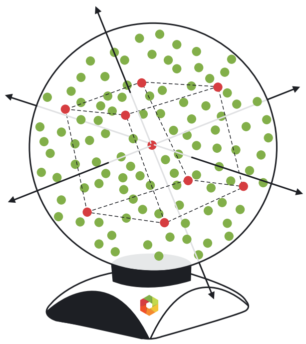
Design of Experiments (DoE) is an invaluable tool to explore important parameters in a chemical reaction. It facilitates the systematic variation of multiple factors simultaneously in a highly efficient and scientifically rational manner. The inclusion of repeated experiments provides an accurate measure of experimental variation and reproducibility in the reactions, whilst statistical analysis allows for the interpretation of the significance of each of the factors investigated in the reaction.

Principal Component Analysis (PCA) is a multivariate data analysis tool which enables the mapping of compounds exploring their relationships to each other and identifying underlying patterns in the data. The mapping converts discreet chemicals into continuous variables of solvents, ligands, Lewis acids or any other compound for which appropriate descriptors that describe the key principal properties can be identified.

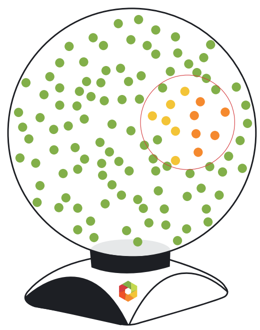
Combining DoE and PCA facilitates the development of a reaction by informed decision, where all critical factors may be considered simultaneously in an efficient and effective manner. The combination of two or more principal properties codes for a reagent. Two or more reagent types can be investigated simultaneously e.g. solvents and ligands in a catalytic reaction.



A set of 100 diverse solvents

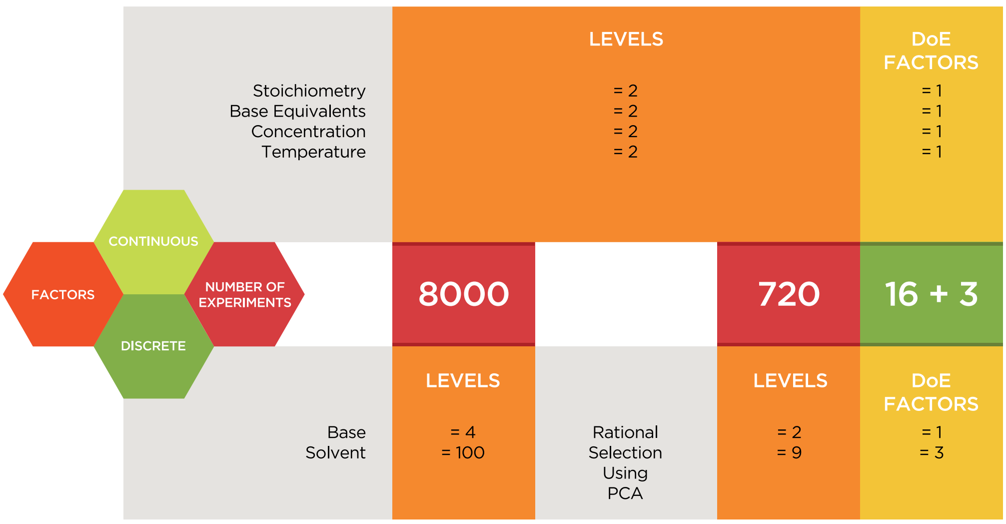


A selection of 9 solvents using PCA



Optimum region identified

It is important to consider that the combination of two or more principal properties provides a near continuous model because a material is unlikely to exist at every point in the two or more dimensions. If three principal properties (PC1, PC2 and PC3) are chosen for a DoE, then the selection of nine reagents, one in each octant and one at the centre, is a sensible way to ensure diverse coverage of chemical space.



An example of combining DoE and PCA for a S_NAr reaction

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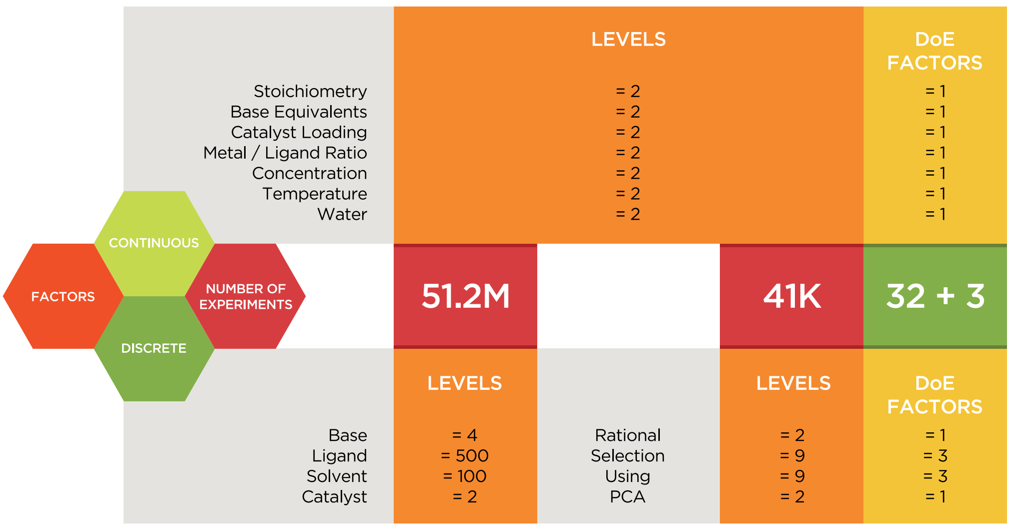
The creation of a DoE which includes PCA can efficiently explore the reaction space to rapidly focus effort into the optimal regions. These designs, like all DoEs, are reliant on the selection of the right factors and the investigation of those factors in the correct range. For a typical reaction there are a number of potentially significant factors to consider. In almost every chemical reaction solvent is one of the factors which can affect, and in many circumstances controls the key aspect of the reaction such as impurities, reaction rates and ease of isolation.

In an example of a S_NAr reaction, four continuous variables were considered alongside two discreet variables which gives a total of 8000 potential experiments. The use of PCA to select 9 representative solvents reduced this to 720 potential experiments and combining PCA and DoE reduced this to 16 experiments plus 3 control experiments to measure reproducibility and accuracy. The initial 19 experiments are unlikely to provide the optimal final solution. However, they will provide a significant insight into the importance of each of the factors investigated in the reaction and the suitability of the explored ranges. This allows all future work to be carried out in the optimal region.

A catalytic reaction is more complicated than most traditional chemical reactions. The inclusion of a catalyst and ligand adds a number of additional continuous and discreet variables that require consideration. The examples below, for a typical Suzuki reaction considering only palladium catalysis, shows how 7 continuous and 4 discreet variables can be explored initially with 32 experiments plus 3 control experiments. This is far more efficient that considering 41,000 or 51 million experiments.



An example of combining DoE and PCA for a catalytic reaction

We have significant experience of combining PCA with DoE. We have employed these techniques for solvent selection, recrystallization, reaction optimisation and the development of catalytic reactions. A number of case studies on the use of PCA and DoE in chemical reactions are available.

In summary the use of DoE and PCA facilitates the development of a reaction by informed decision, where all critical factors may be considered alongside one another in an efficient and effective manner. This methodology has been proven in a diverse range of projects and can be a central tool in addressing the challenge of Quality by Design.

Paul Murray Catalysis Consulting provides Consulting and Training in Design of Experiments (DoE), Principal Component Analysis (PCA), homogeneous, heterogeneous and biocatalysis.

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