AI4X – Accelerate Conference 2026: Dynamic Parameter Scanning: a Novel Method for Mechanistic Elucidation

Dylan Pyle,[1,2] Finn Bork,[*1,2] Joshua Derasp,[1,2] Wesley McNutt,[1,2] Ekaterina Trushina[1,2], Matthew Mower,[3] Jan Dijkmans[3] and Jason Hein[1,2,4]

[1] Department of Chemistry, University of British Columbia, Vancouver, British Columbia, Canada [2] Acceleration Consortium, University of Toronto, Toronto, Ontario, Canada [3] Chemical Process Research and Development, Janssen Pharmaceuticals, Turnhoutseweg 30, Beerse 2340, Belgium [4] Department of Chemistry, University of Bergen, Bergen, Norway

Correspondence to: dpyle@chem.ubc.ca

Introduction:

Mechanistic elucidation studies currently follow a sequential one factor at a time (OFAT) perturbation approach. These OFAT experiments are used for a Variable Time Normalization Analysis (VTNA)[1]. VTNA relies on the visual overlay differences between experiments to be directly represented by the changes in concentration of the perturbed reagent which is not always the case due to complexities in the reaction network. The consequences of overlooked complexities and a sequential approach called for a change in protocol to accelerate and deepen understanding. Here we are reporting DPS (dynamic parameter scanning) which parallelizes mechanistic studies. DPS works by following a series of re-additions of reagents and catalysts to an ongoing reaction to understand the effect of each reagent on the chemical system.

Alongside the synthetic method development we also developed modeling software for quantitative model fitting to the unique DPS timecourse curves. These DPS timecourses provide unprecedented insight to the underlying reaction mechanism and aid model fitting for complex chemical reactions.

We have applied this DPS protocol for understanding Kumada Cross Coupling's across three different Palladium catalysts. This was chosen as the model system due to the unique curvature of time courses and inconclusive VTNA results.

Results and Discussion:

As a starting point of this investigation, we collected a VTNA suite on our Kumada system using Pd-XPhos-G2 as a catalyst (Fig. 1) The results were inconclusive due to poor overlap on ⅔ of the VTNA overlays. Based on that, we were unable to conclude quantitative information on the order in each reagent or catalyst.

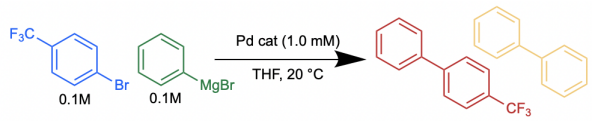

Fig. 1: Kumada system we studied. Pd cat was changed across different reactions between Pd-DPPF, Pd-XPhos-G2, and PEPPSI-Ipr.

The important caveat to VTNA graphical elucidation of orders is that overlay is required[1]. Without proper overlay the information cannot be obtained quantitatively. From our VTNA plots we were able to gather that the Grignard is heavily inhibitory, the arylhalide is critical for having an active catalyst, and that the catalyst concentration plays a strong role in the rate of reaction, but the value of orders for each reagent remained unknown.

To run a standard VTNA suite of experiments on the system shown in *Figure 1*, one needs to run a minimum of four duplicate or triplicate experiments to understand order in catalyst, order in reagent A, and order in reagent B. It brings the total number of experiments to at least eight. VTNA experiments require a high level of precision and small perturbations from human error can render these experiments obsolete. We overcame the limitations of VTNA in our studies and we were able to harness all the information from a VTNA suite in one DPS experiment.

It should be noted that all experimental data collection for both VTNA and DPS studies was performed in automated fashion using DirectInject-LC™ (DILC) system, which enables direct online sampling and HPLC analysis of chemical reactions. This technique significantly accelerates mechanistic elucidation.

Each DPS experiment was accompanied by a standard condition reaction, *Fig. 2,* to understand the rate of reaction in order to inform a user on how to plan the DPS experiment.

The development of a standard DPS protocol called for both modelling and synthetic insights. From the modelling side it was deemed critical that each starting material must approach close to zero concentration at various times throughout the dynamic experiment. Modelling also informed us to decide that a minimum of five time points must be taken between re-additions to account for various curvature types that could arise in kinetic studies. From the synthetic side it was important for the scientist to maintain control

over the reaction. This means that the reaction must run slow enough for the scientist to be able to make strategic on the fly decisions for re-additions.

With both modelling and synthetic necessities in mind we have created a standard DPS protocol for A + B systems like the Kumada:

Start: excess of reagent A, let reagent B approach zero before re-addition.

Addition 1: Add Reagent B in large excess, let reagent A approach zero.

Addition 2: Add Reagent A such that B stays in Excess.

Addition 3: Add product or by-product that may play a role in catalytic behaviour.

Addition 4: Add catalyst, sample until reaction terminates.

Notes: the additions can be in different order depending on catalytic behaviour. Decisions can be made on the fly based on domain expert intuition.

We have executed these DPS experiments across three different catalysts for Kumada cross couplings to highlight the versatility of this method in mechanistic understanding and catalytic activity.

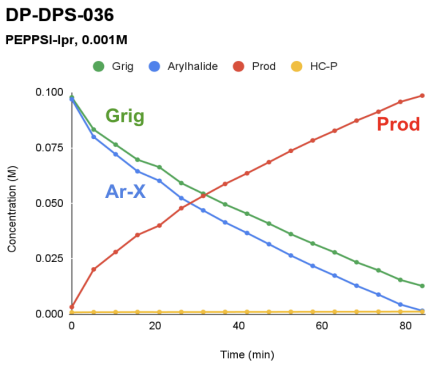

Fig. 2: Standard experiment with PEPPSI-Ipr as the catalyst.

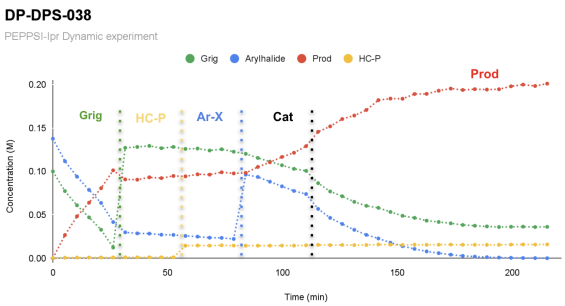

Fig. 3: Example DPS experiment with PEPPSI-IPr. *Regime 1:* zero order behaviour. *Regime 2:* reaction stalled with Grignard in large excess. *Regime 3:* No change from by-product addition, *Regime 4:* restarts zero order regime at slower rate with Grignard in excess. *Regime 5:* catalyst re-addition caused a change from zero order to exponential decay.

Pd-DPPF, Pd-XPhos-G2, and PEPPSI-Ipr were studied with DPS and we were able to harness all the information equivalent to a VTNA suite in two experiments across these three different catalysts:

PEPPSI-Ipr: the reaction follows a zero order trend when the aryl-halide is in excess, the catalyst is heavily inhibited by the Grignard reagent, and the catalyst will behave as zero order until pushed past a certain threshold in concentration.

Pd-DPPF: Catalyst is deactivated by excess bromide, forming a palladate species with the oxidative addition complex. The rate limiting step is transmetallation and the off cycle process is similar in forward and reverse rates to the rate limiting transmetallation step. Grignard helps to drive this reaction forward by forcing the slow step to be more productive.

Pd-XPhos-G2: Reaction has a high turnover followed by a zero order plateau period followed by a rate increase when Grignard reagent is depleted. Catalyst is deactivated by excess Grignard. Catalyst increases reaction rate when readded to the system. This catalyst provides a large amount of grignard homocoupling relative to the other catalysts.

Conclusion

DPS is a novel framework for accelerating mechanistic studies. This approach decreases the amount of experiments a scientist needs to run to understand their chemical system. This approach was developed using our re-addition modelling software package, Easymax reactors for automated execution and DILC for online analysis. With DPS we were able to accelerate the understanding of the impacts each reagent has on a chemical system. All the answers a scientist could want from a traditional mechanistic study can be obtained from one dynamic experiment. Additionally, the length of these DPS experiments is longer than standard OFAT experiments, which provides scientists with information on catalyst longevity which could have been previously overlooked. The DPS experiments also provide direct insight to how ongoing reactions respond to readdditions.

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References

[1] Dr. Jordi Bures, Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles, Angewandte, 16084-16087, 2016.