New Approaches to *in situ* Analysis of Reactions by NMR and IR

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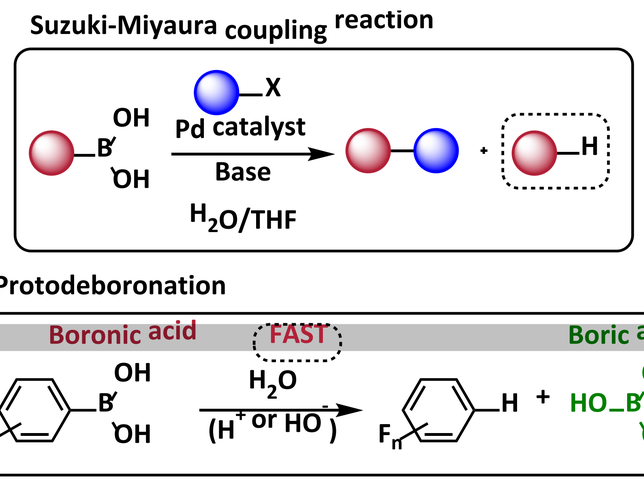
Introduction

Mechanistic understanding allows us to control reactions, establishing optimum conditions to reduce by-products, increase yields and improve reaction selectivites. Ultra fast reactions are difficult to study, and therefore control.

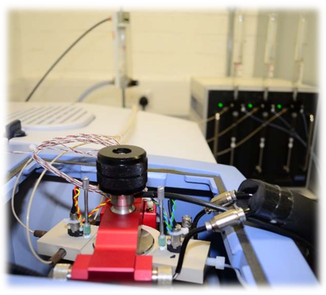
The Suzuki-Miyaura cross-coupling reaction is a palladium-catalysed bond-forming reaction, coupling a boronic acid with an electrophile. The boronic acids can protodeboronate, reducing yields and efficiencies of the cross-coupling. In the case of poly-fluorophenyl boronic acids, this is extremely fast and renders the cross-coupling impracticable.

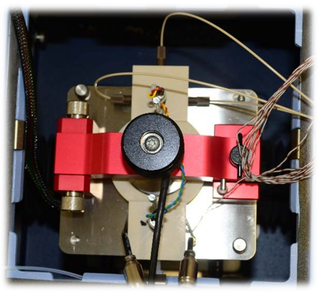
Stopped-flow (SF) techniques can be used to study this extremely fast reaction, propose a mechanistic model and identify optimum conditions for the effective cross-coupling.

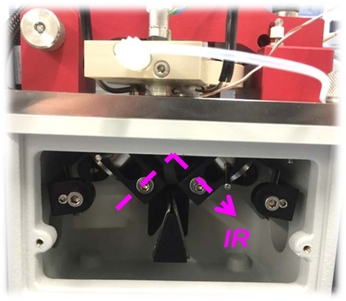


Data Acquisition

IR





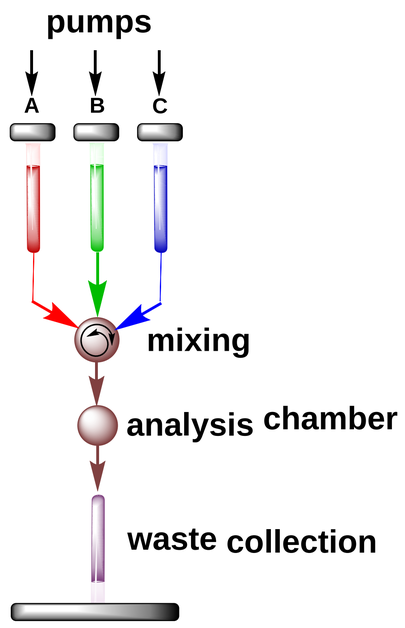


Reagent syringes driven by independent pumps.

Flow rates of up to 2 ml/s allow fast mixing.

Data acquisition is triggered by syringe drive.

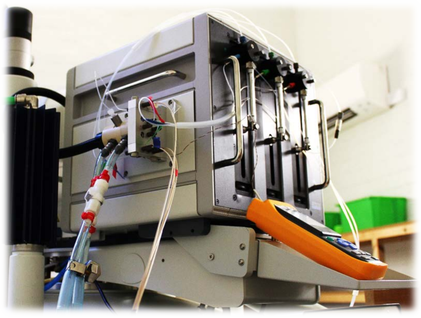
A second shot clears the analysis chamber and initiates next reaction.



NMR

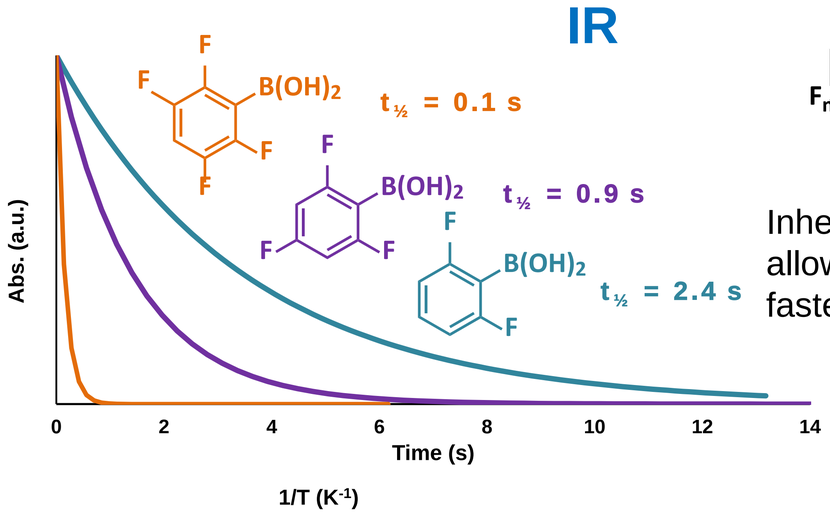
Reagent lines and mixing cell are premagnitised and thermostatted.

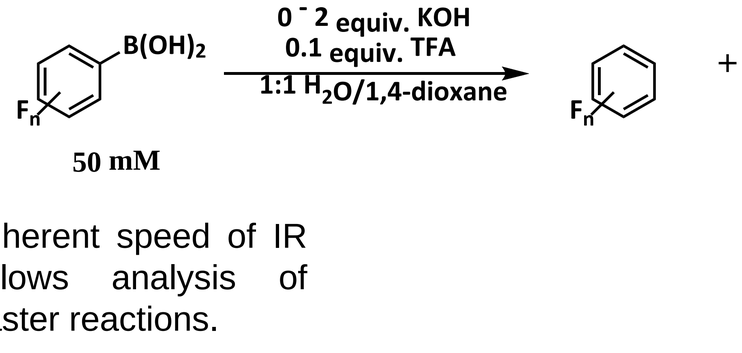
- ✓ Reduced dead time.
- ✓ Single stock solution.
- ✓ Multiple repeats + conditions.
- ✓ Accurate temperature control.
- ✓ Reduced error.



Results

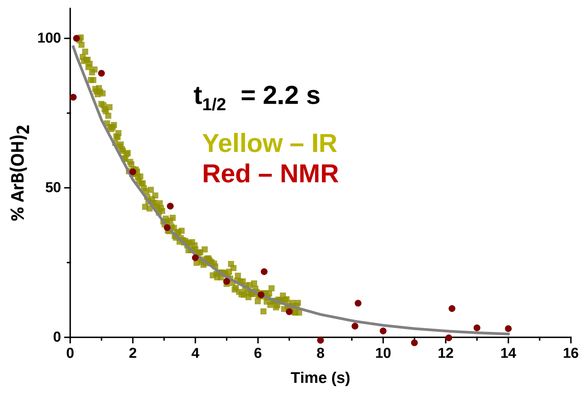
IR



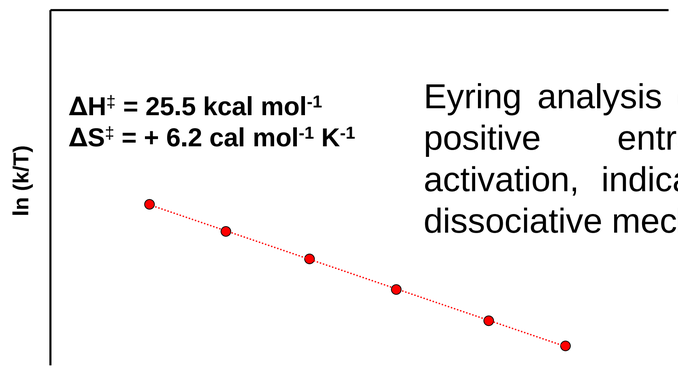


50 mM

Inherent speed of IR allows analysis of faster reactions.

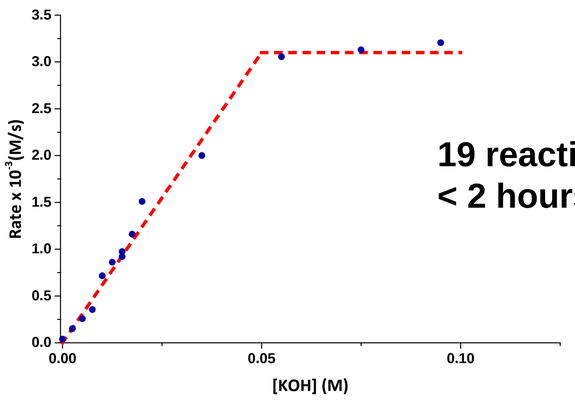


Combination of the two techniques allows cross-validation.



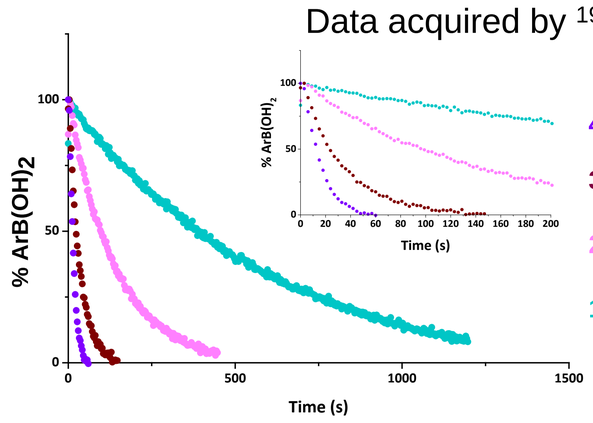
Eyring analysis displays a positive entropy of activation, indicative of a dissociative mechanism.

NMR



19 reactions
< 2 hours

Data acquired by ^{19}F NMR



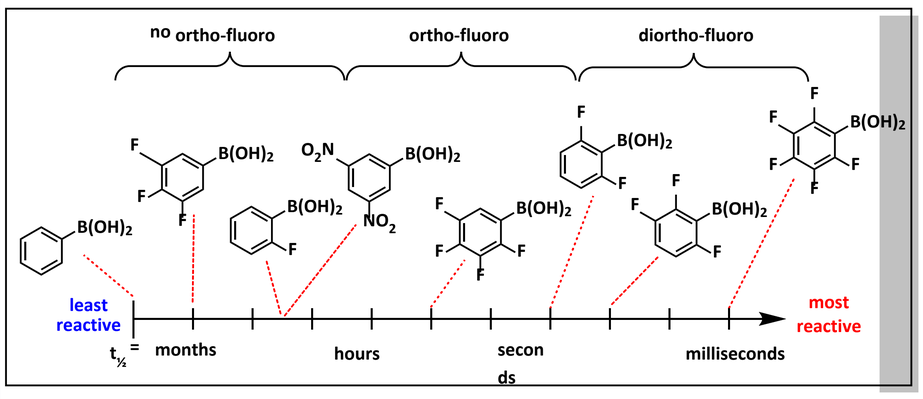
40 °C $t_{1/2}$ = 9 s

30 °C $t_{1/2}$ = 22 s

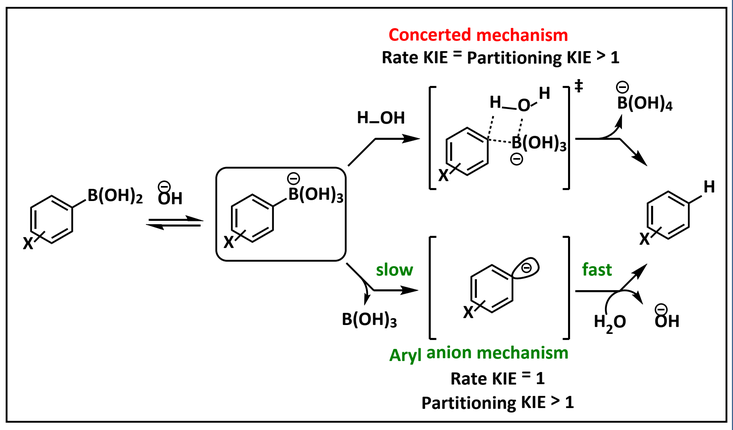
20 °C $t_{1/2}$ = 95 s

10 °C $t_{1/2}$ = 368 s

Conclusions



- Stop flow (SF) techniques allow fast, reproducible monitoring of fast reactions, with accurate temperature control.
- SF-NMR and SF-IR have allowed a complete mechanistic study of the deprotonation of poly-fluorophenyl boronic acids.
- Fast deboronations proposed occur via a stabilised aryl anion, due to the inductive influence of the fluorines.



References

Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. *J. Am. Chem. Soc*. **2016** DOI: 10.1021/jacs.6b03283.
Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. G.; Lloyd-Jones, G. C. submitted, **2016**.