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SNUG PG NMR course, Edinburgh

3rd December 2024

Reaction monitoring using NMR spectroscopy

Annabel Flook, Roisin O'Dea

Studying reactions by NMR

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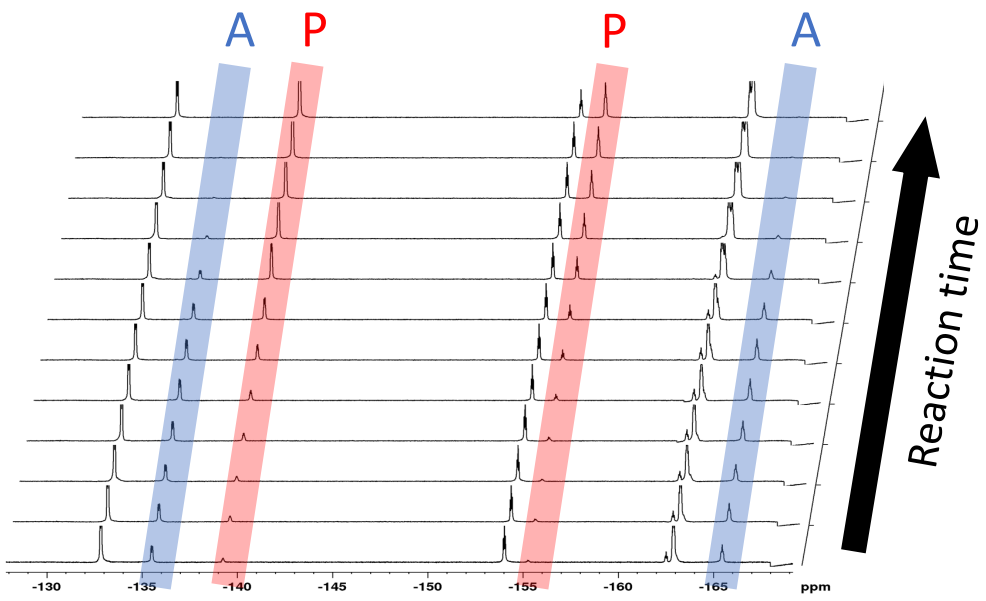
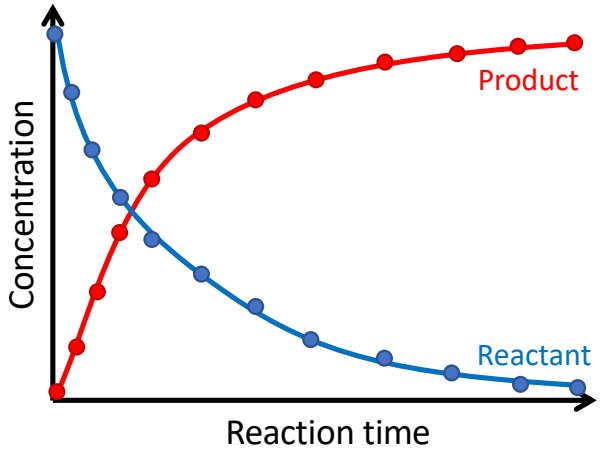
Spectra acquired periodically during reaction time

A → P





Overview

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- Solvent
- Nucleus
- Quantitative NMR
  - Internal standard
    - T_1 measurement
- Monitoring methods
  - *Ex-situ*
  - *In-situ*
  - Interrupted

Solvent and nucleus choice

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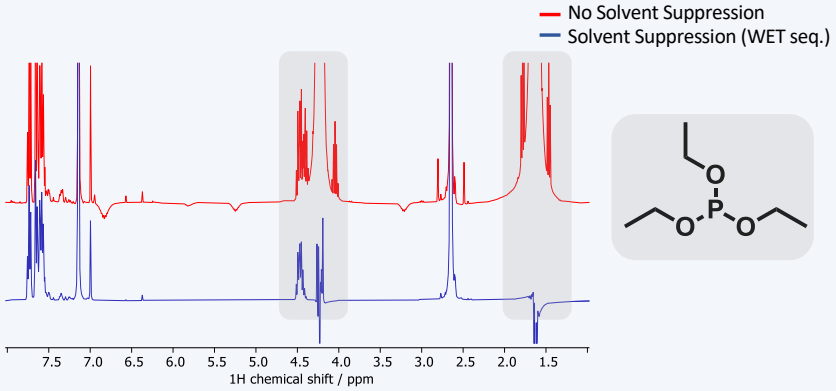
Homogeneous

Temperature

Cost

Protonated solvents

- ✓ Cheaper/scalable
- ✓ Solvent suppression possible



Deuterated solvents

- ✓ Chemical Shift reference
- ✓ No large ^{1}H solvent signals

Nucleus	Relative sensitivity
^{1}H	**100%**
^{13}C	1.6%
^{19}F	**83.4%**
^{31}P	6.7%

Cat. Sci. Tech. ***2016, 6 (24), 8406-8417.***

Internal standard

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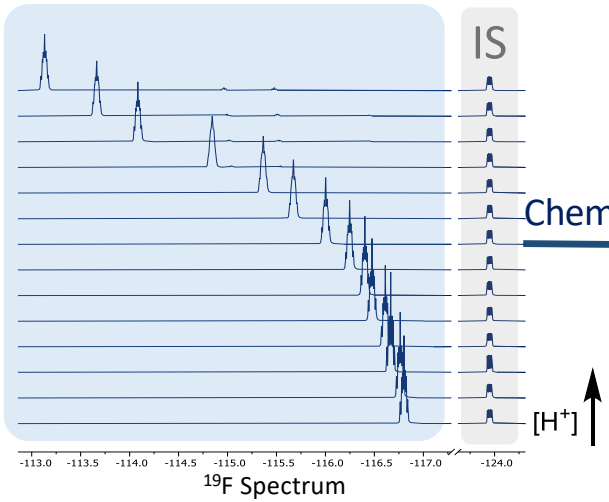


Chemical Shift

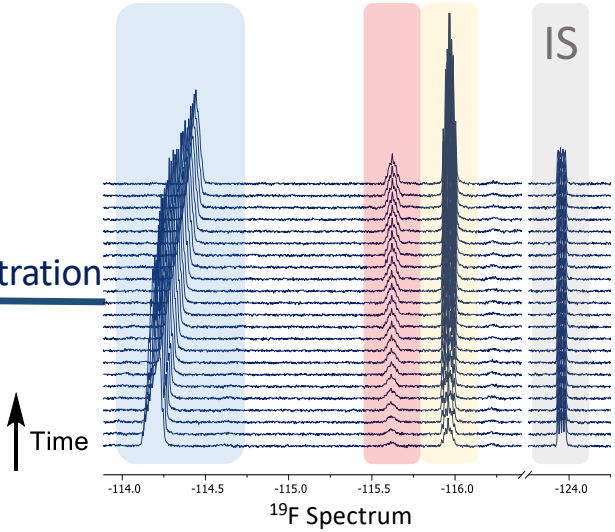
[H$^+$]

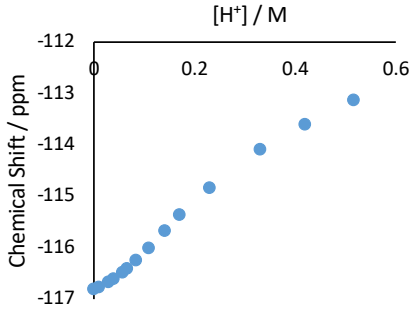
Internal standards:

- ✓ Inert in reaction
- ✓ Soluble
- ✓ Non-volatile
- ✓ Well resolved signal
- ✓ Known concentration

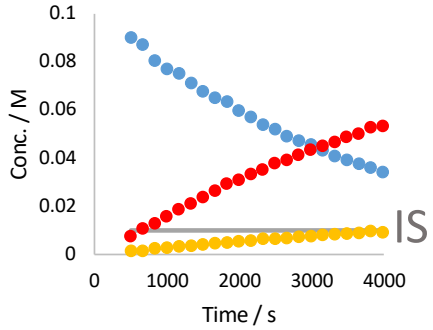
Concentration

Time





Compound	Nucleus	Chemical shift (ppm)
1,3,5-Trimethoxybenzene	^{1}H	6.09, 3.77
1-Fluoronaphthalene	^{19}F	-123.95
Fluorobenzene	^{19}F	-113.15
(p-tolyl)$_3$P=O	^{31}P	29.20



Prog Nucl Magn Reson Spectrosc, ***2022,*** *129,* 28.

Quantitative NMR

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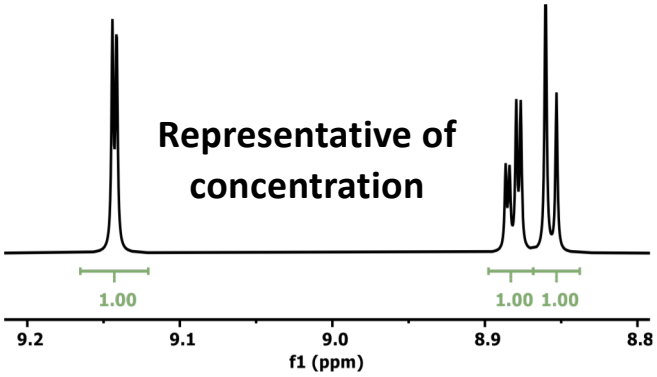
Sufficient delay ($5xT_1$) must be left between every pulse to ensure quantitation.

Appropriate delay (~ $5xT_1$)



Quantitative NMR

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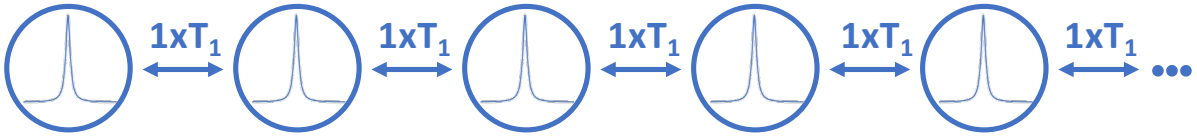
Sufficient delay ($5xT_1$) must be left between every pulse to ensure quantitation.

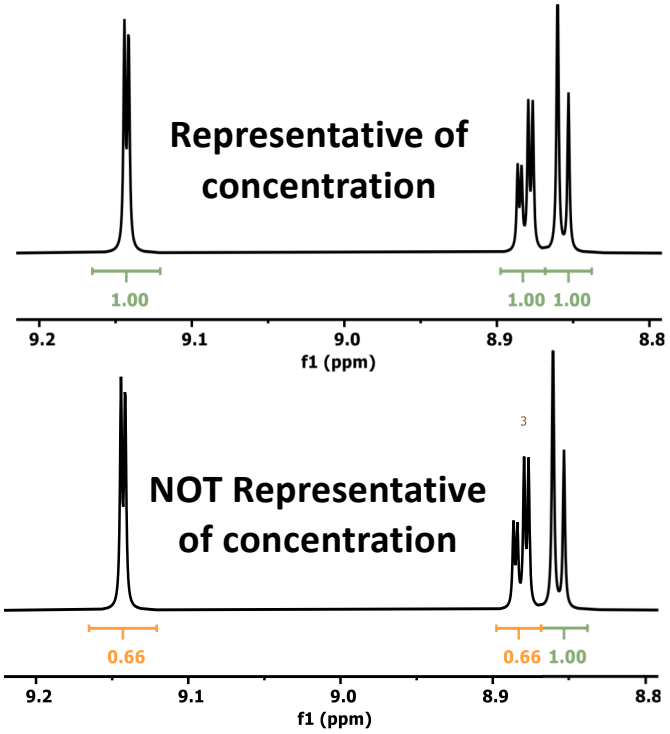
T_1's can:

- Be different for every peak
- Change with temperature
- Change with solvent
- Change when degassed

Appropriate delay (~ $5xT_1$)

Too short





Overview

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Solvent

Nucleus

Quantitative NMR

- Internal standard
- T_1 measurement

Monitoring methods

- *Ex-situ*
- *In-situ*
- Interrupted

Monitoring methods

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Monitoring methods

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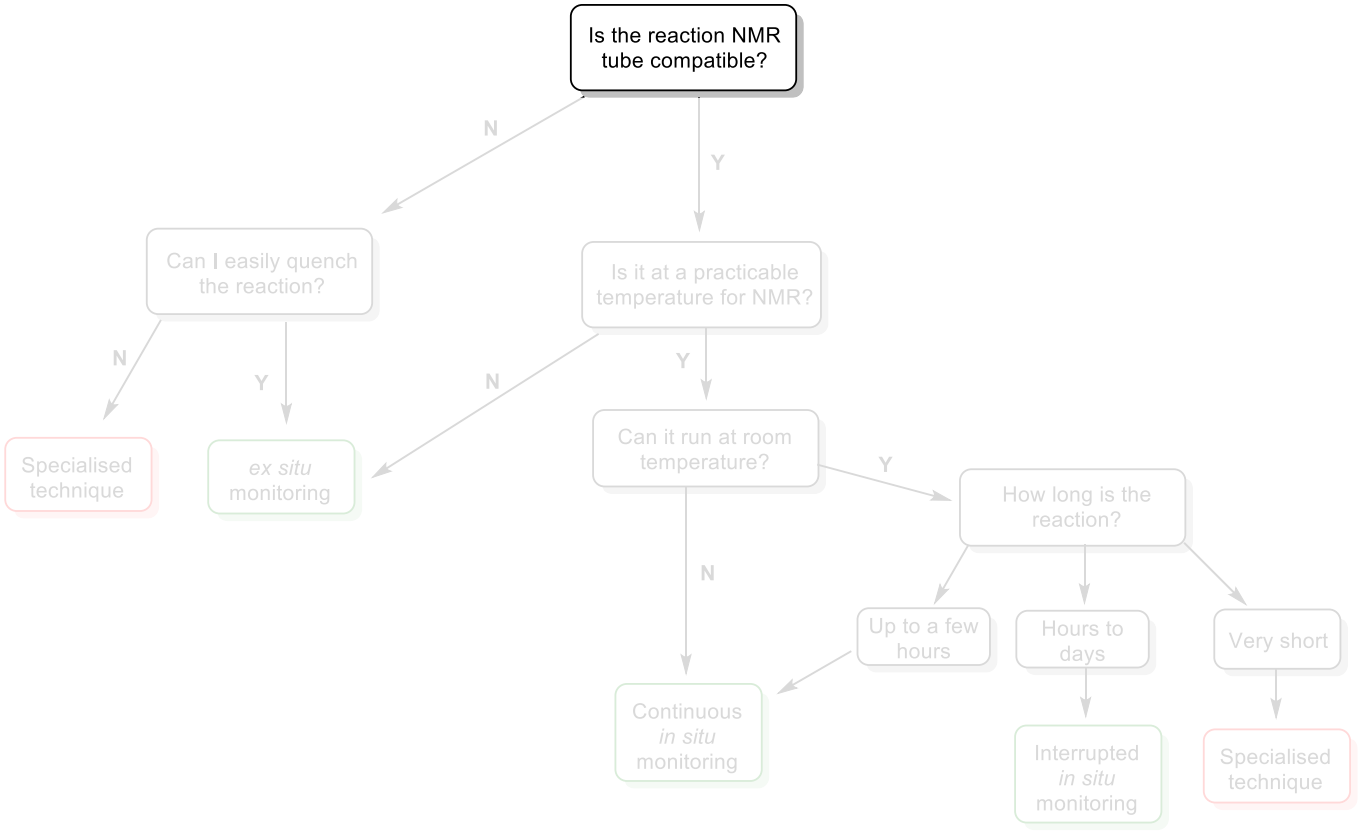

Monitoring methods

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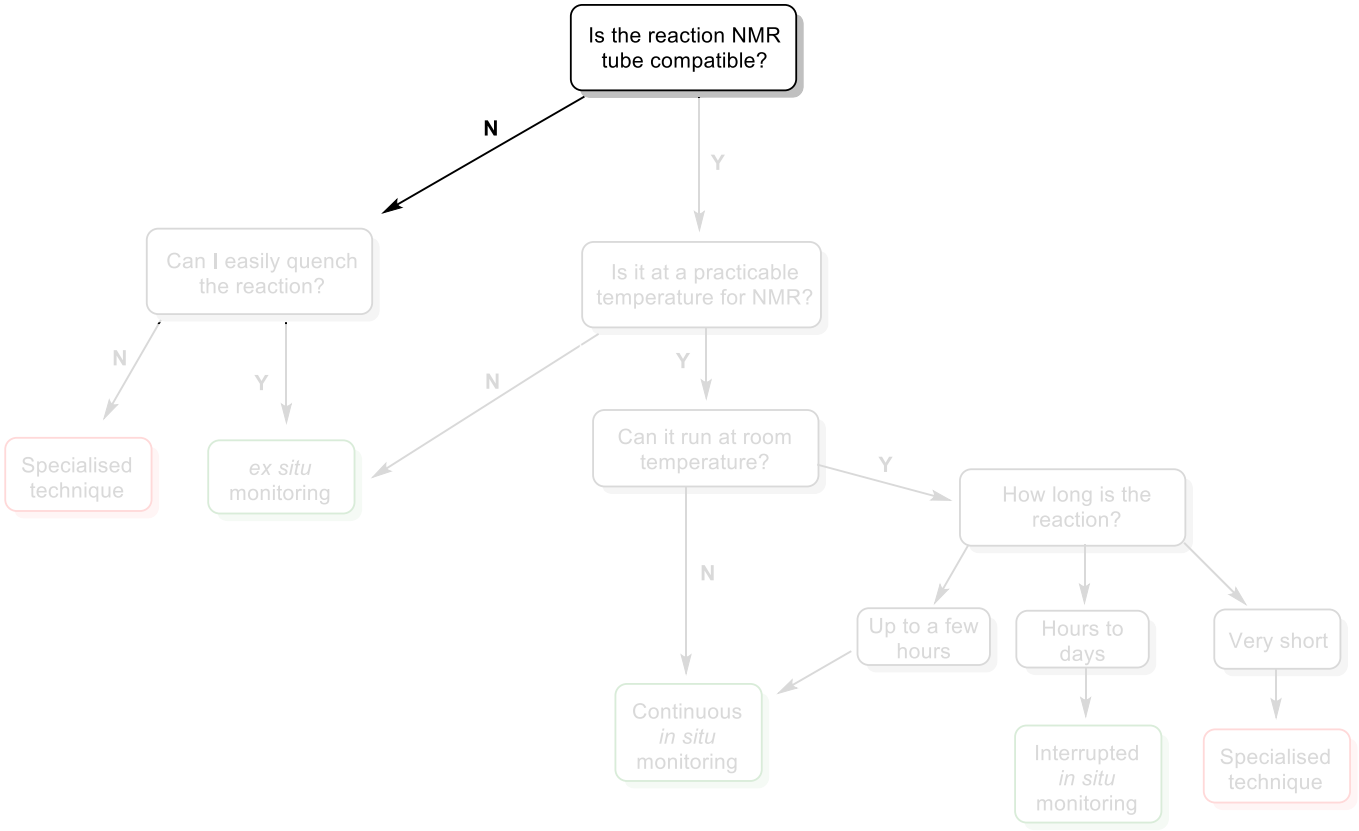

Monitoring methods

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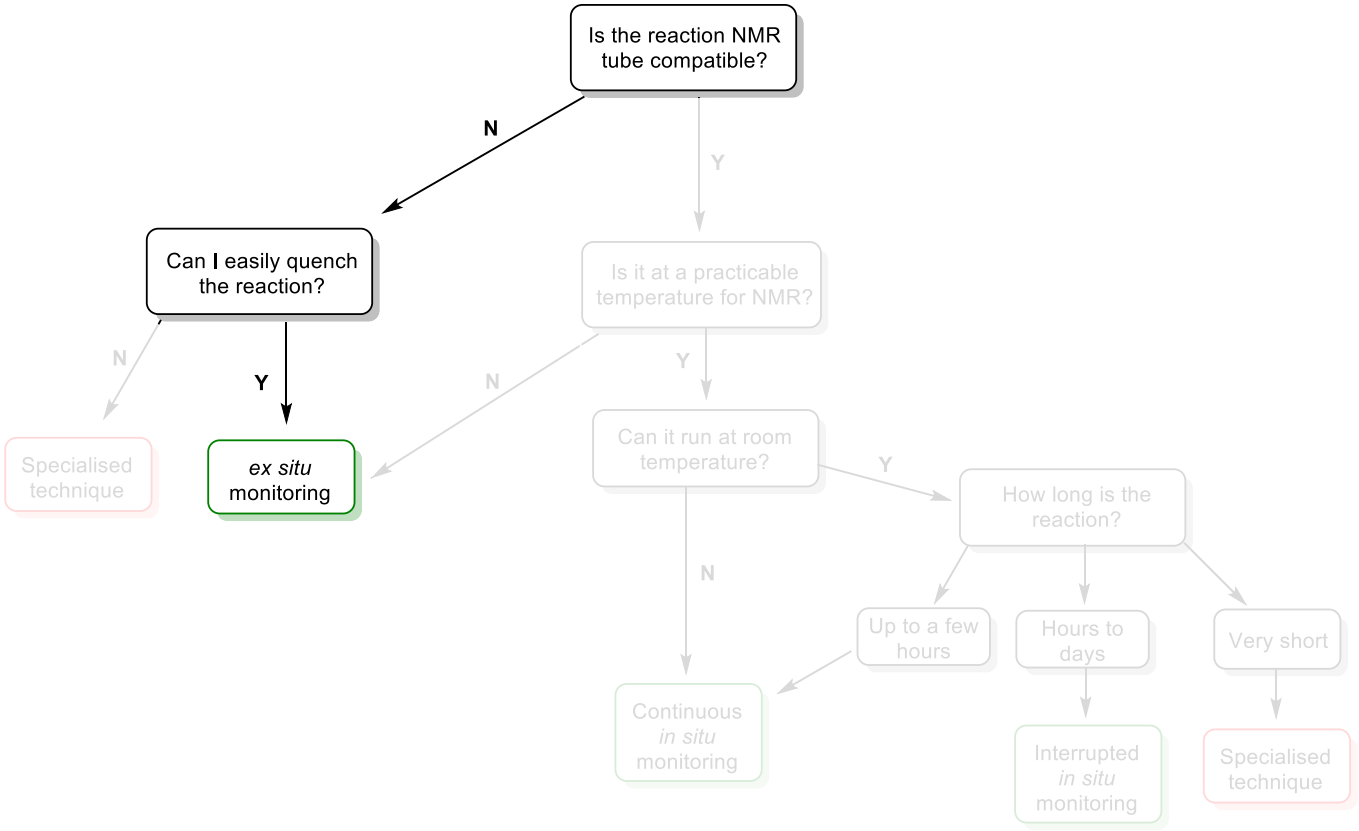

Monitoring methods

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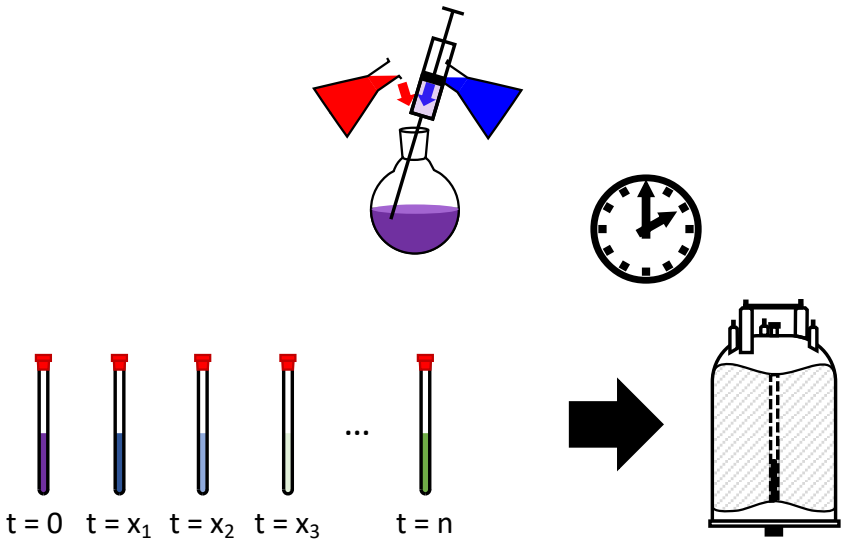
Ex-situ



- ✓ Real reaction conditions
- ✓ Heterogeneous possible
- ✓ Mixing
- ✗ Labour intensive
- ✗ Quenching required

Monitoring methods

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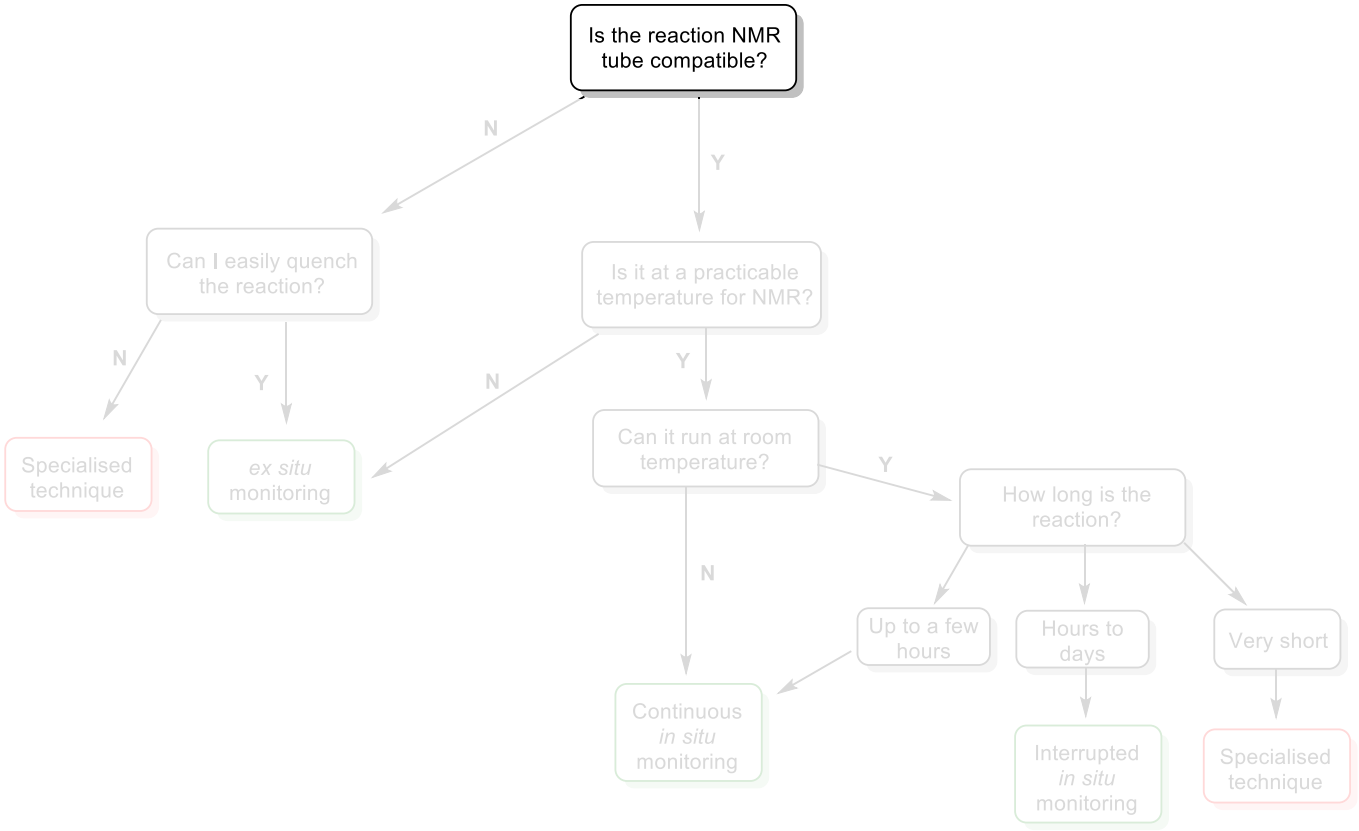

Monitoring methods

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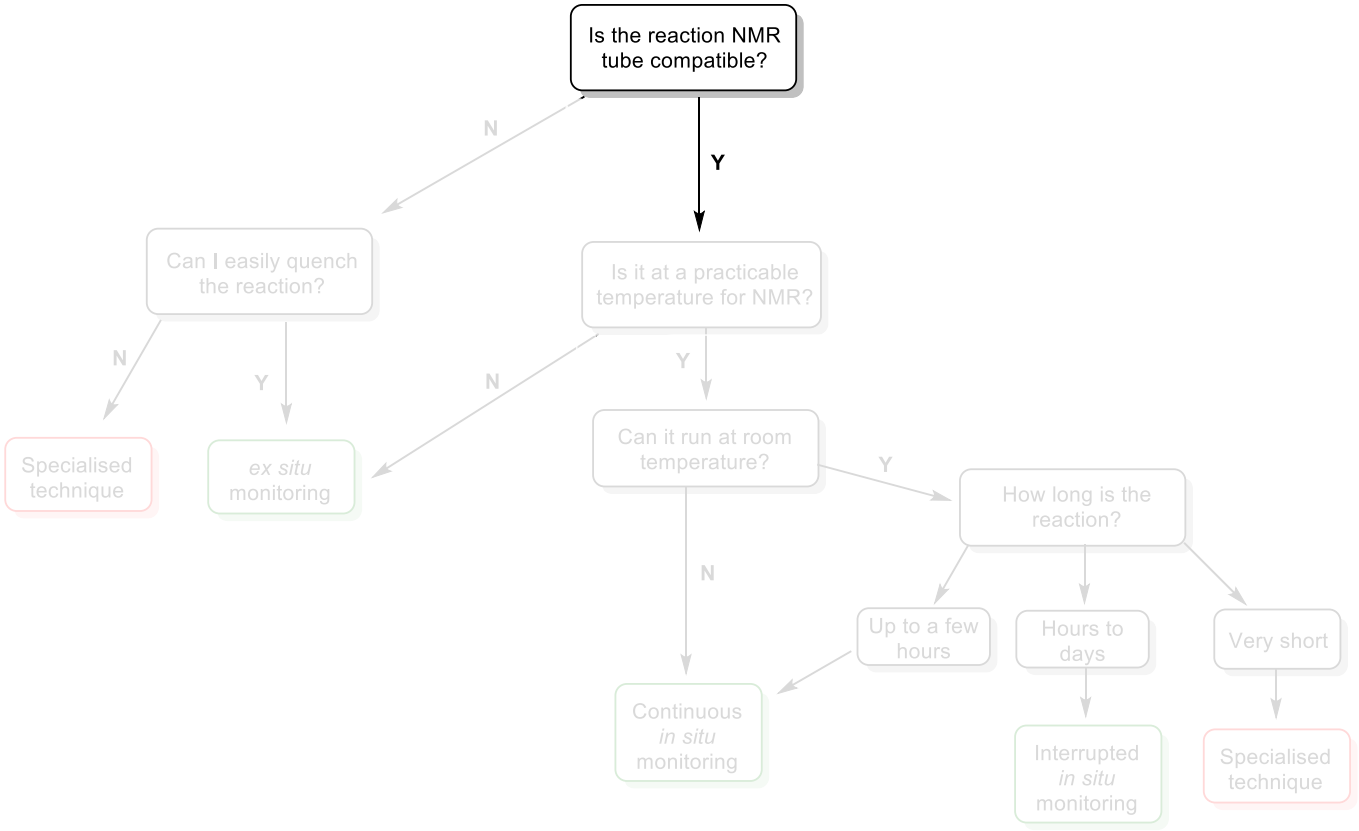

Monitoring methods

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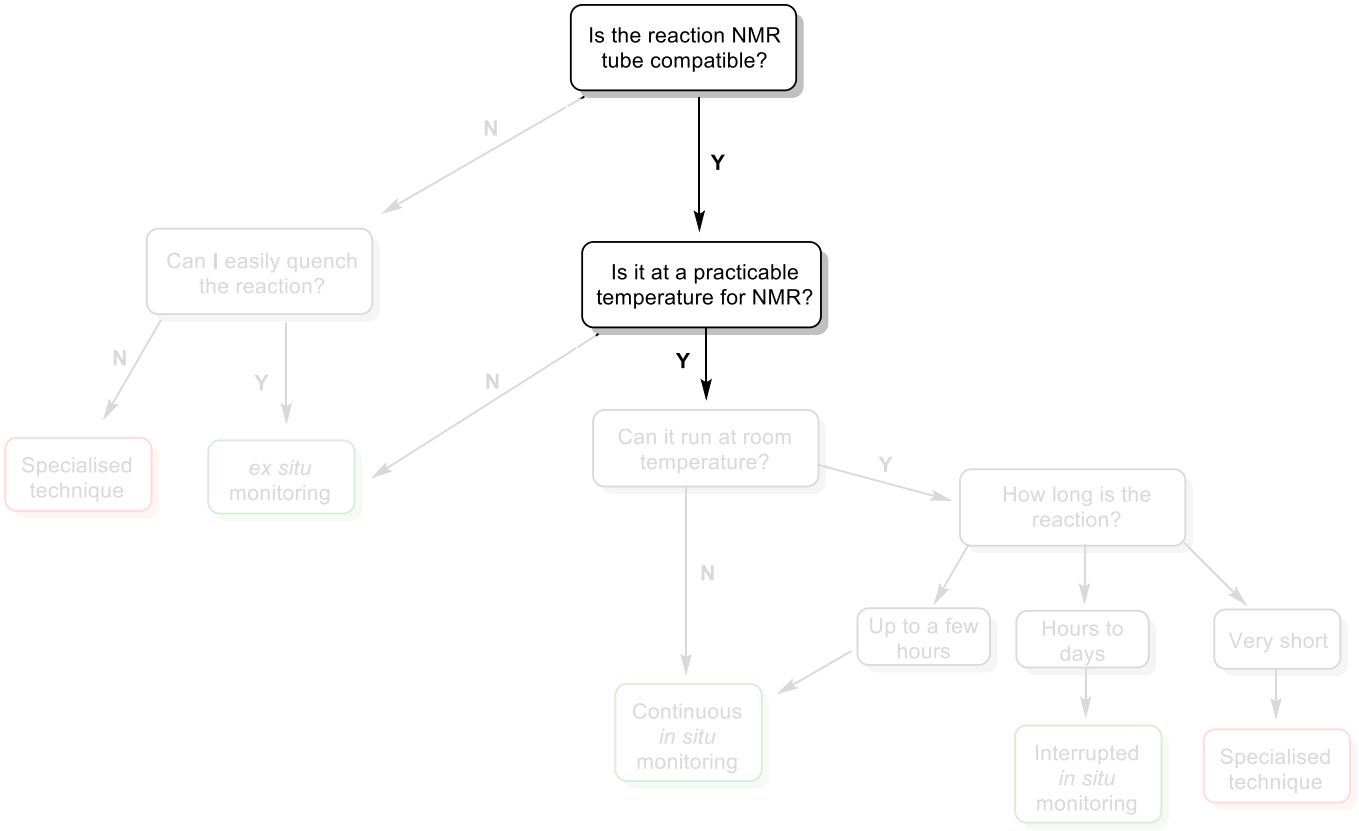

Monitoring methods

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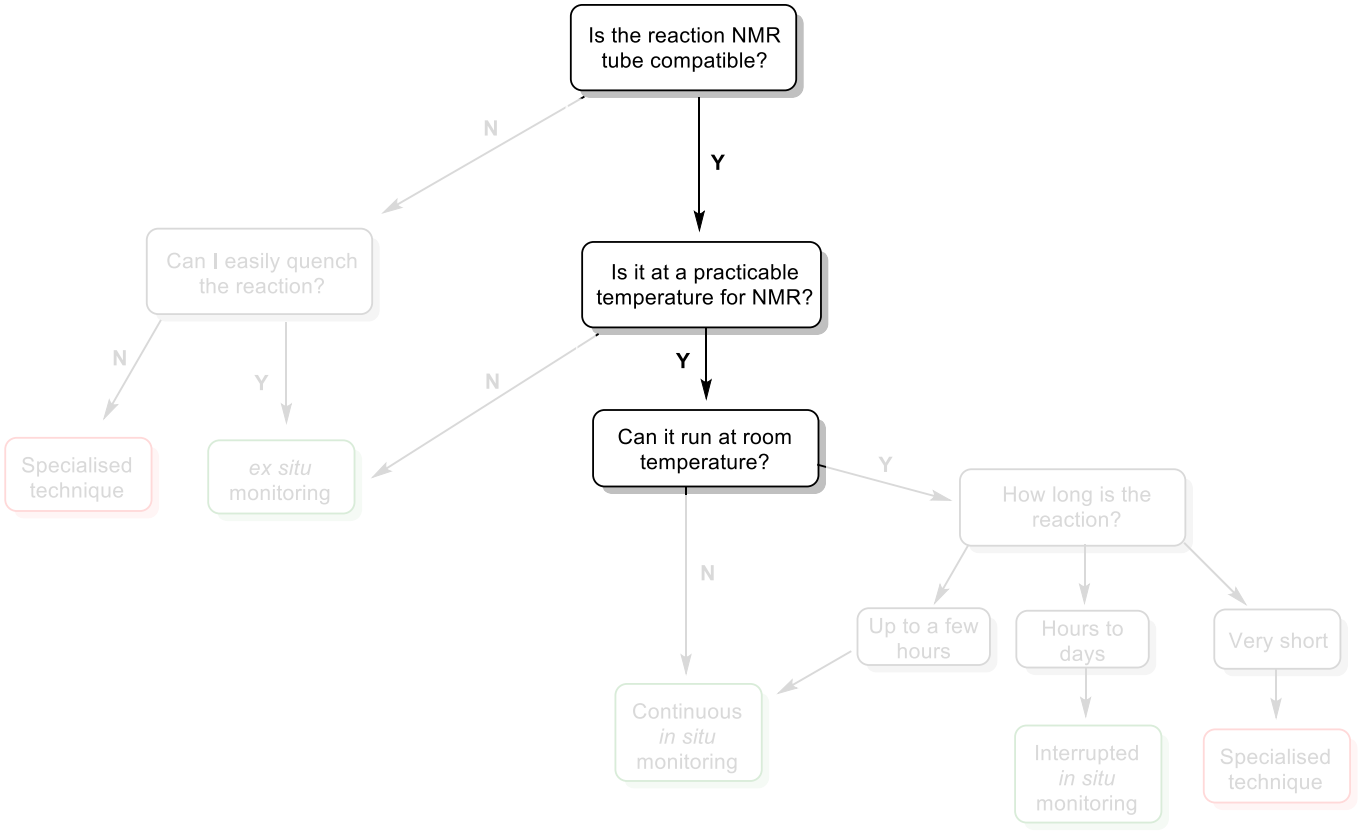

Monitoring methods

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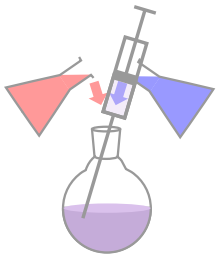
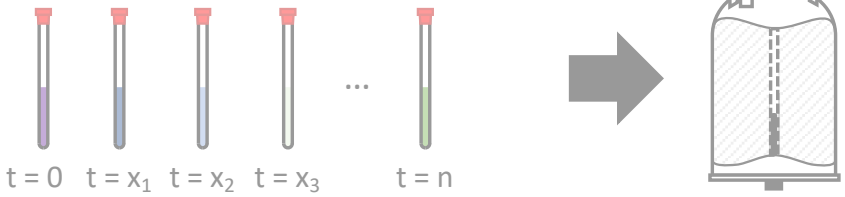
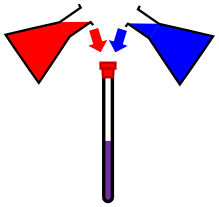
Ex-situ

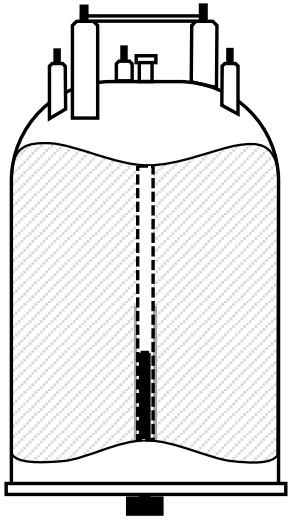




- ✓ Real reaction conditions
- ✓ Heterogeneous possible
- ✓ Mixing
- × Labour intensive
- × Quenching required

In-situ





- ✓ Easy to set up
- ✓ Temperature control
- ✓ No quenching needed
- × No constant mixing
- × Homogeneous only

Monitoring methods

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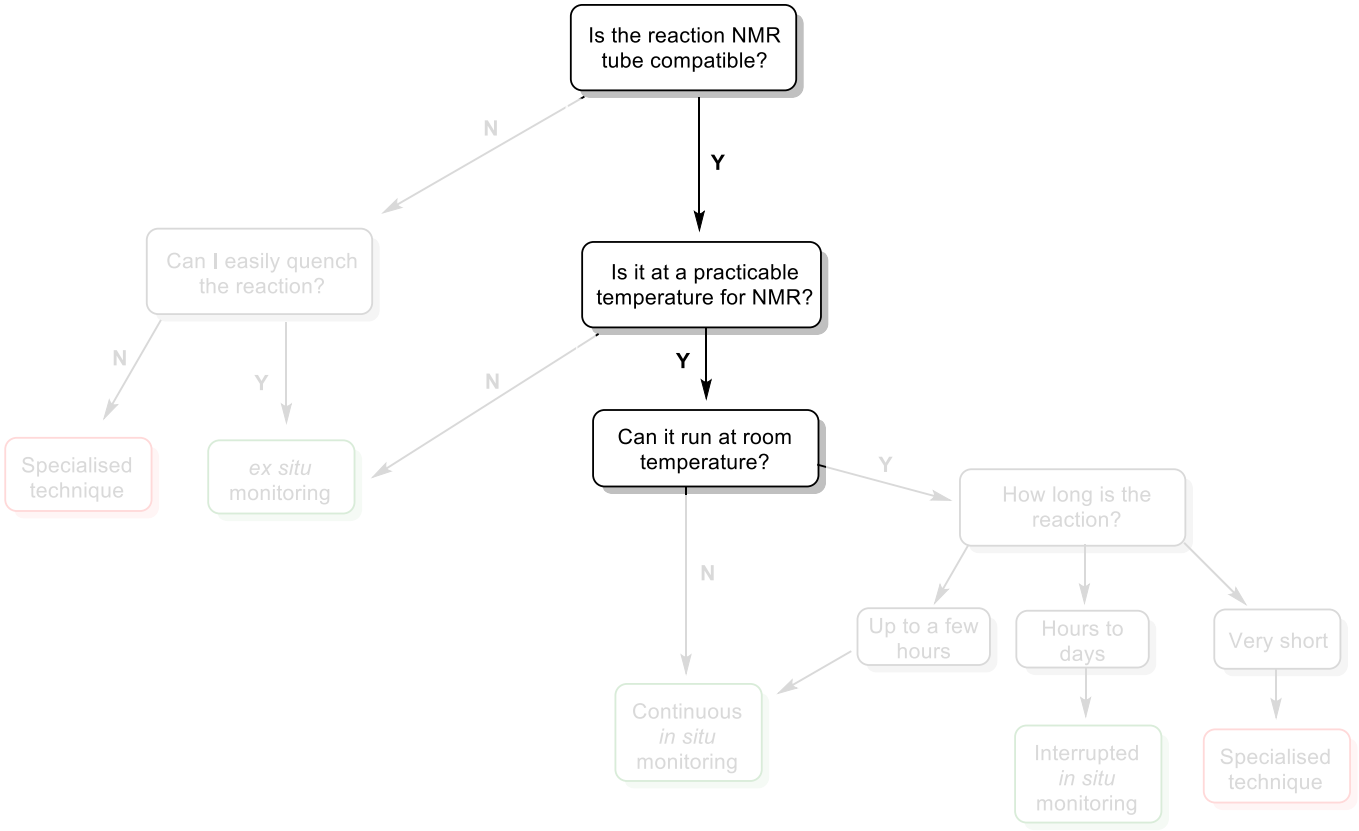

Monitoring methods

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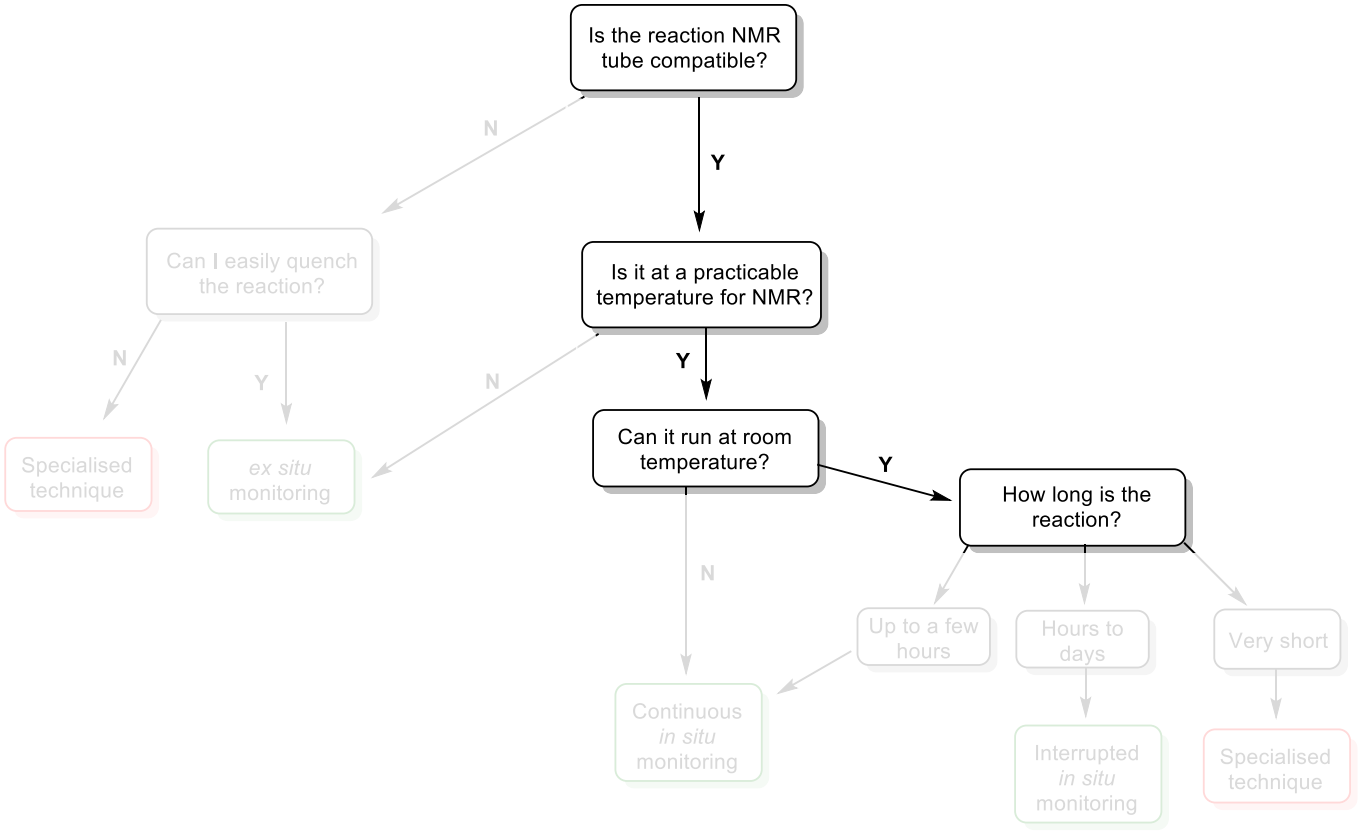

Monitoring methods

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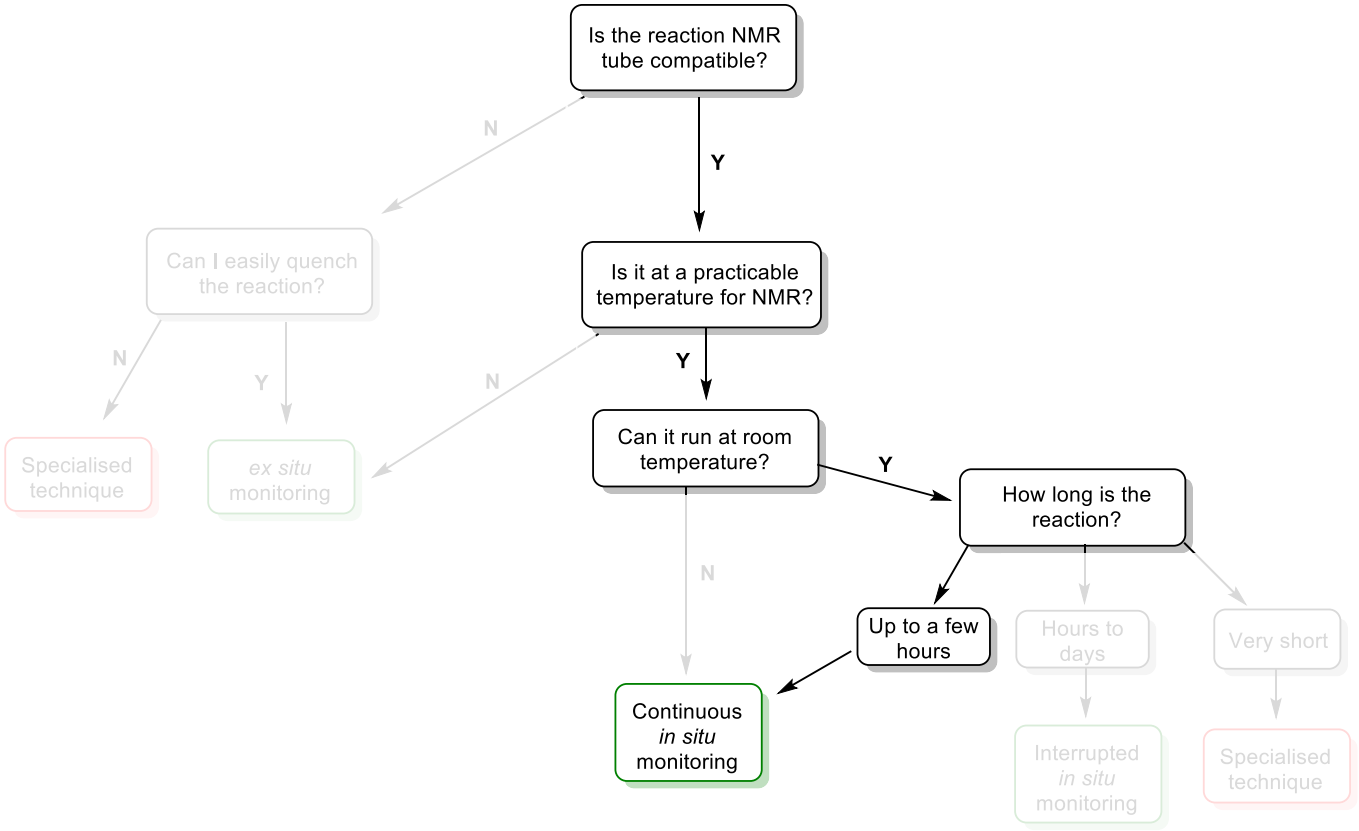

Monitoring methods

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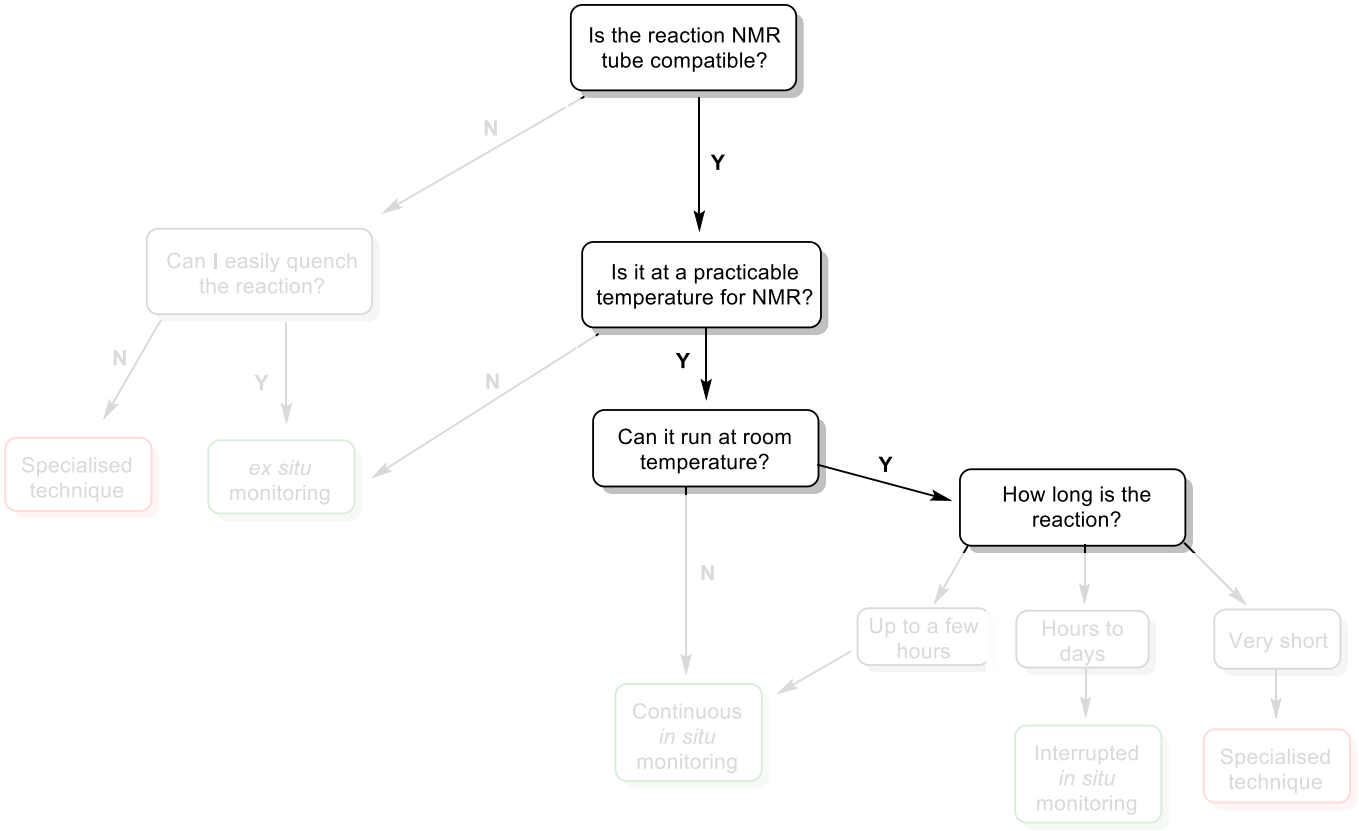

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Case study:
Protodeboronation of boronic esters

Hayes *et al., J. Am. Chem. Soc.* 2021, 143, 36, 14814–14826

Protodeboronation of boronic esters

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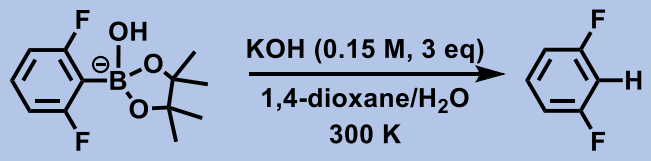


Intermediate?

What do we need?

- ☑ Solvent (deuterated/non-deuterated)
- ☑ Monitoring method
- ☐ Internal standard
- ☐ T_1 measurement

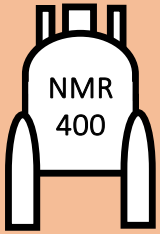
Homogeneous

Room temperature

Hours

^{19}F NMR possible

Monitoring method



In-situ

Protodeboronation of boronic esters

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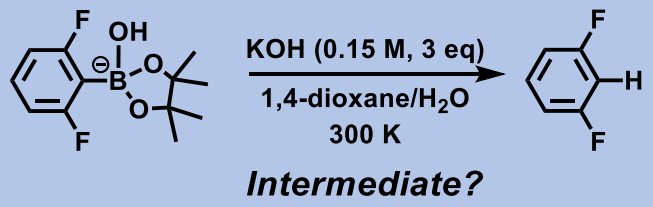

Intermediate?

What do we need?

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- ☑ Monitoring method
- ☑ Internal standard
- ☐ T_1 measurement

Homogeneous

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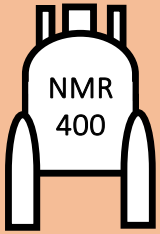
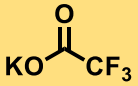
Monitoring method



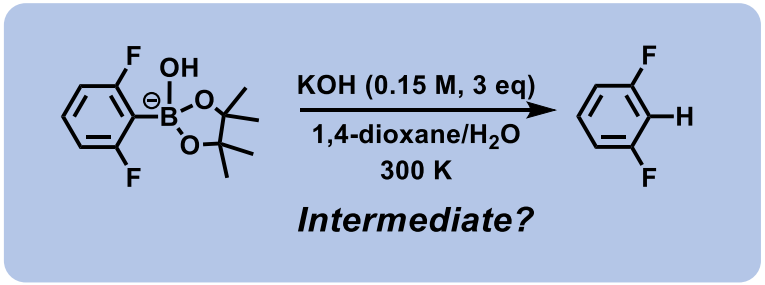
In-situ

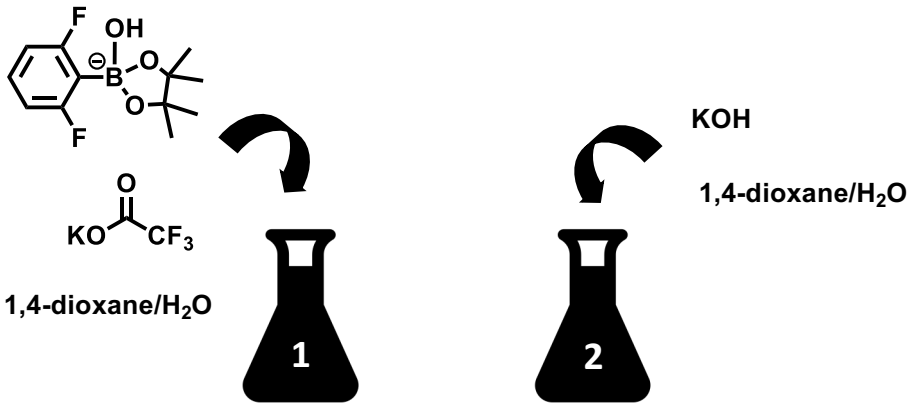
Internal standard

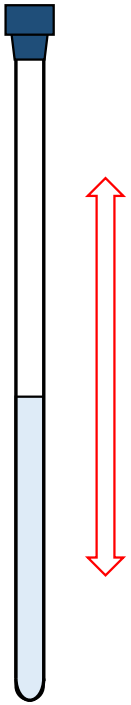


- ✓ inert
- ✓ soluble
- ✓ non-volatile
- ✓ well resolved peak

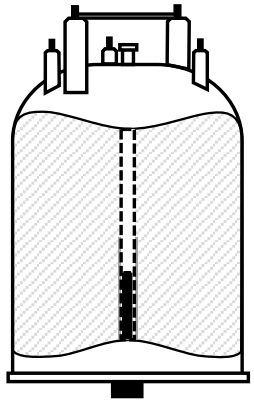
Sample preparation



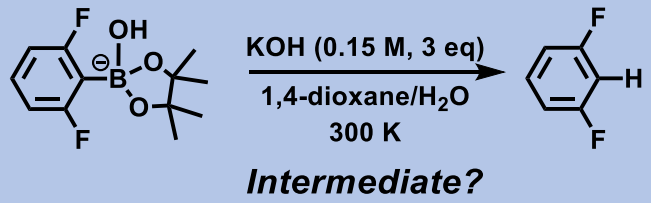


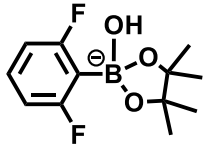


dummy sample



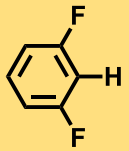
T_1 measurements and Monitoring





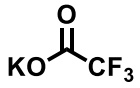
Starting material

T_1 = 0.6 s



Product

T_1 = 1.8 s



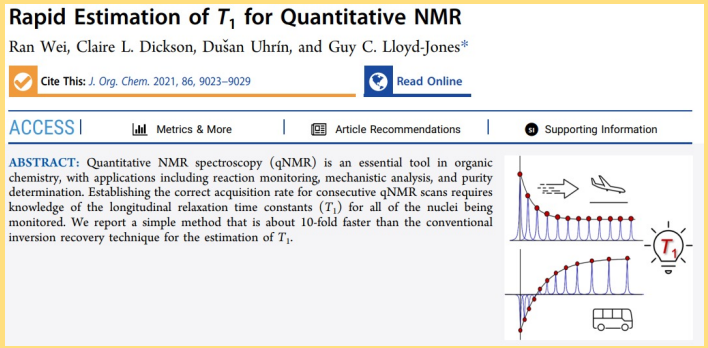
Internal Standard

T_1 = 1.4 s

Delay ≥ 5 x T_1 **1.8 s x 5 = 9 s**

1. Inversion Recovery

2. FLIPS



Rapid Estimation of T_1 for Quantitative NMR

Ran Wei, Claire L. Dickson, Dušan Uhrín, and Guy C. Lloyd-Jones*

Cite This: J. Org. Chem. 2021, 86, 9023−9029 Read Online

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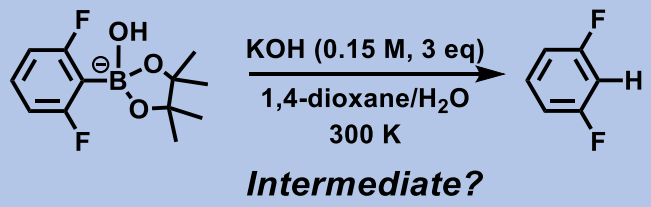
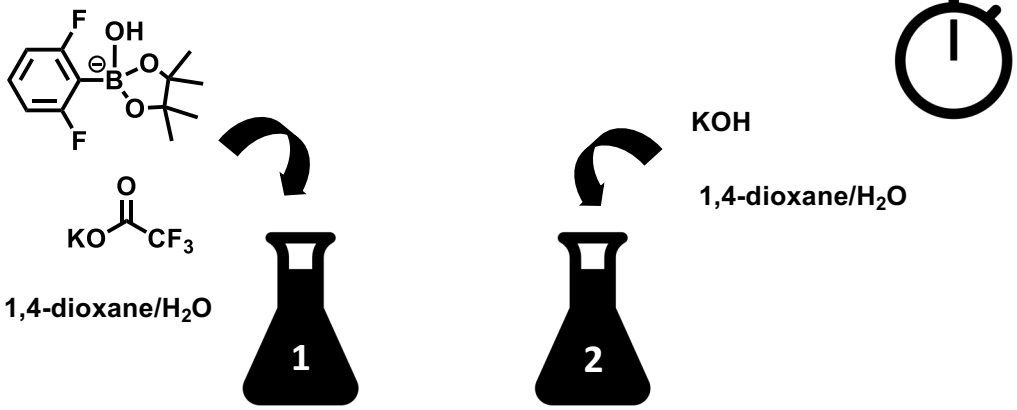
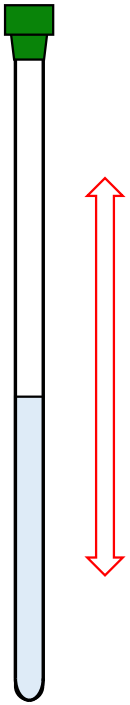
ABSTRACT: Quantitative NMR spectroscopy (qNMR) is an essential tool in organic chemistry, with applications including reaction monitoring, mechanistic analysis, and purity determination. Establishing the correct acquisition rate for consecutive qNMR scans requires knowledge of the longitudinal relaxation time constants (T_1) for all of the nuclei being monitored. We report a simple method that is about 10-fold faster than the conventional inversion recovery technique for the estimation of T_1.

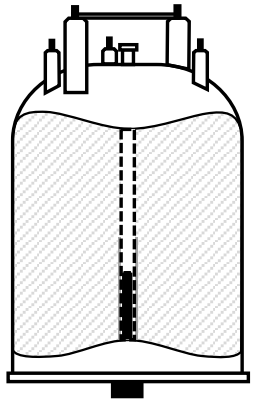
Sample preparation







sample



Data analysis

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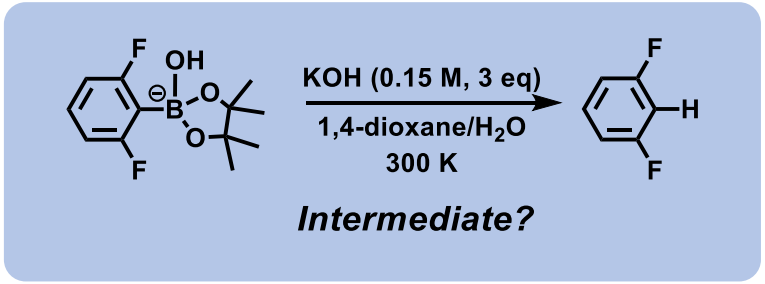
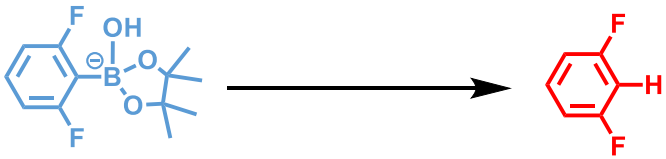
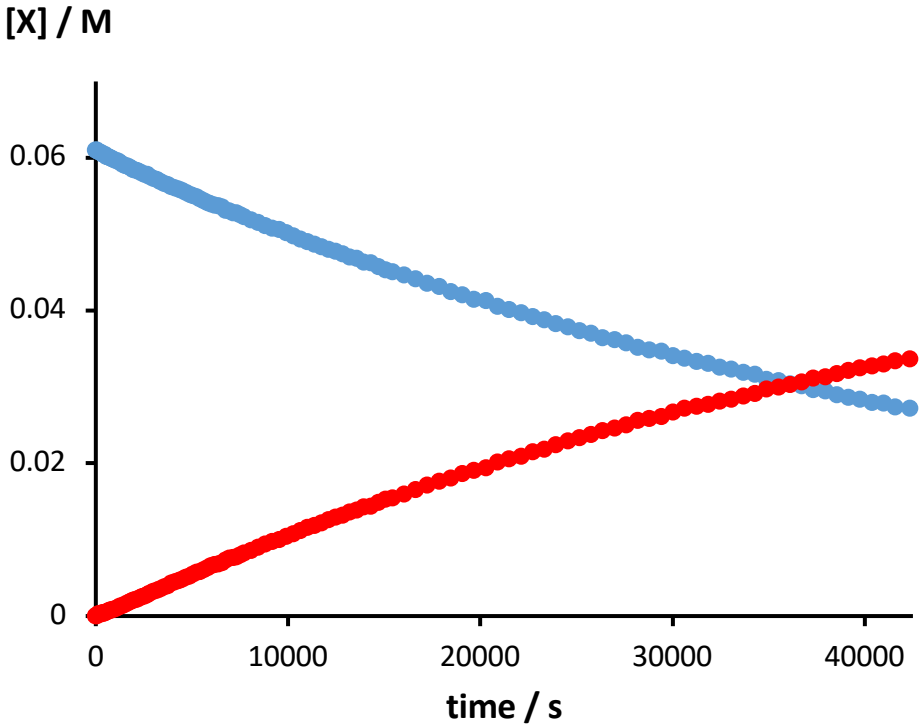
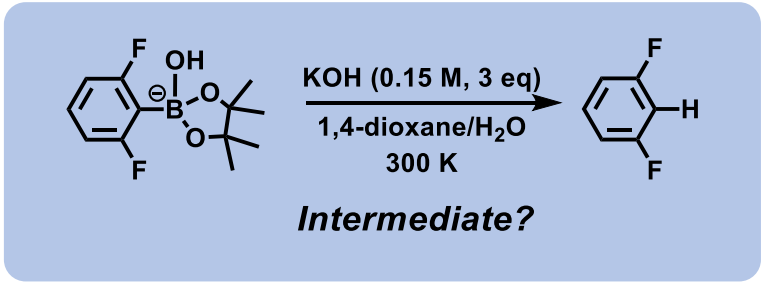
Results

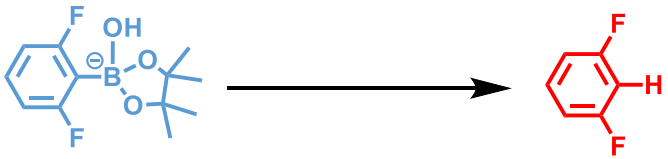

F
OH
B
O
O
F
KOH (0.15 M, 3 eq)
1,4-dioxane/H2O
300 K
F
H
F
Intermediate?

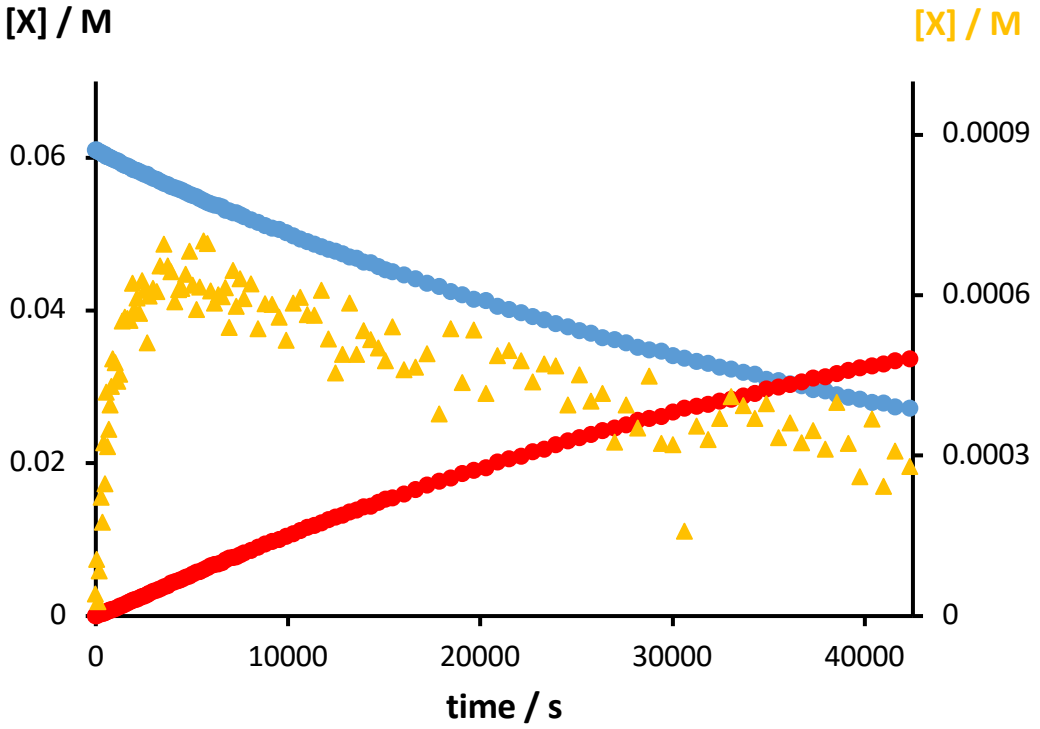

F
OH
B
O
O
F
F
H
F


[X] / M
0.06
0.04
0.02
0
0
10000
20000
30000
40000
time / s

Results


F
OH
B
O
O
F
KOH (0.15 M, 3 eq)
1,4-dioxane/H2O
300 K
F
H
F
Intermediate?


F
OH
B
O
O
F
F
H
F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[X] / M
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0.04
0.02
0
0.0009
0.0006
0.0003
0
0
10000
20000
30000
40000
time / s

Overview

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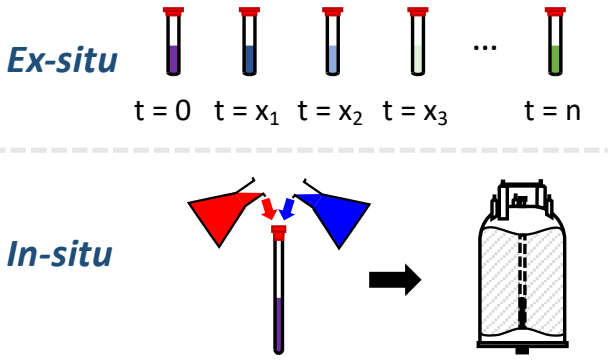
Important Check-List

- □ Solvent/Nucleus
- □ Internal standard
- □ T_1 measurement

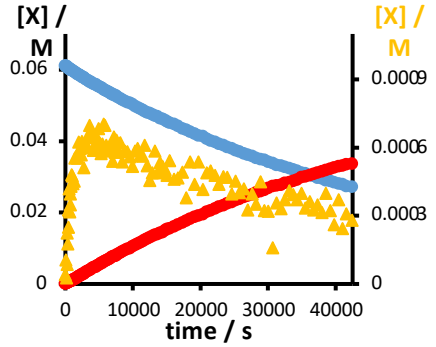
⬇

- ✓ Reaction Profile
- ✓ Kinetics
- ✓ Intermediates

Monitoring Methods



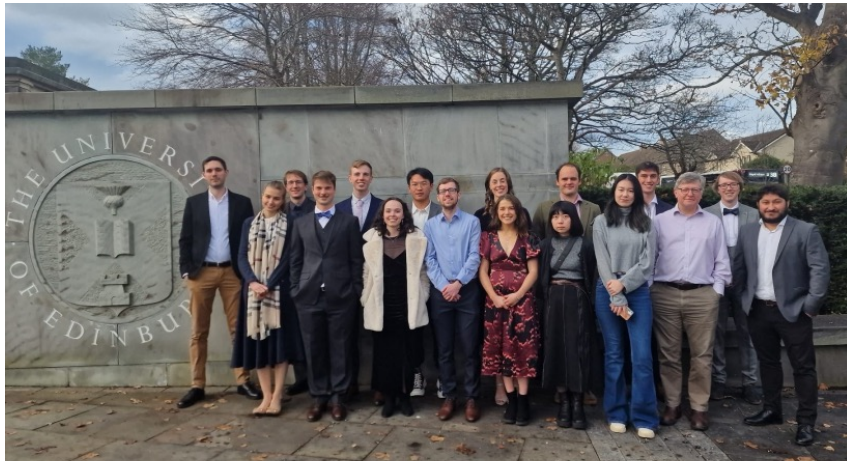
Case Study



RESOURCES AND LITERATURE

"Mechanistic analysis by NMR spectroscopy: A user's guide"
Prog. Nucl. Magn. Reson. Spectrosc., **129**, 28–106, **2022**

NMR Facility Managers



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