Integrating Benchtop NMR into synthesis workflows: A path from Manual Sampling, over on-line monitoring of a biphasic reaction, towards AI-Enabled Self-Optimization of a flow process

Harald Todt, Jasmin Wloka, Hélène Freichels, Jürgen Kolz, Federico Casanova, Magritek GmbH
(Magritek GmbH, Philipsstraße 8, Aachen, Germany)
Harald@magritek.com

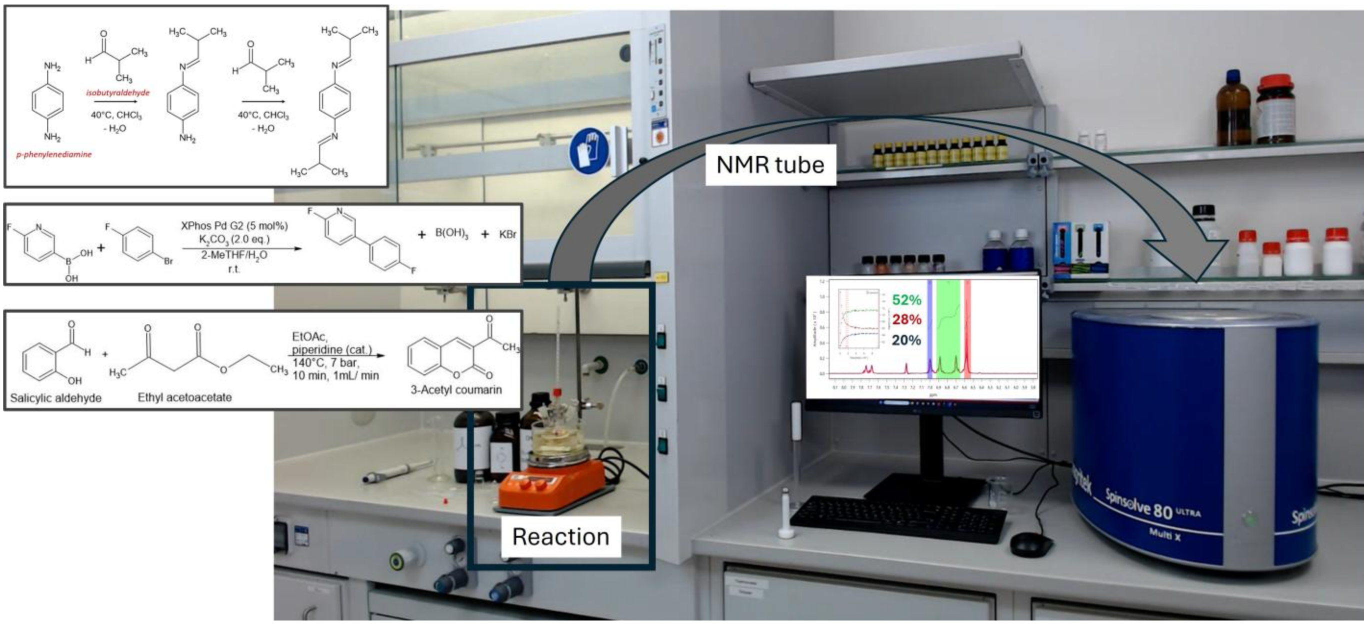
No-D (non-deuterated solvent) NMR spectroscopy enables routine structural analysis using standard laboratory solvents, eliminating the need for expensive deuterated reagents[1]. This technique provides a convenient and robust approach for directly monitoring reaction mixtures in their native solvents. We demonstrate that $^{1}H/^{11}B/^{19}F$ No-D NMR performed on benchtop instruments provides synthetic chemists and chemical engineers with immediate structural information that is directly accessible in routine laboratory work and equally applicable to scale-up and production environments. The scope of information obtained underscores the method's suitability for regular use across these operational scales [2].

The utility of the method is illustrated through several representative applications: (1) Monitoring the formation of Schiff bases between phenylenediamine and isobutyraldehyde, in which the final product and the intermediate species were tracked using manual sampling and continuous-flow setups; (2) Tracking different nuclei in a biphasic Suzuki-cross coupling reaction, following both starting materials in their respective solvent (water phase and organic solvent phase) in parallel with two Spinsolves and (3) Examining a Knoevenagel condensation between salicylic aldehyde and ethyl acetoacetate to produce 3-acetylcoumarin in a flow reactor, including fully automated reaction-condition optimization using Bayesian algorithms. In this workflow, the Spinsolve instrument automatically reports conversion values after each change in reaction conditions to external software, which then computes and applies the subsequent set of conditions for the next optimization step.

These applications demonstrate that No-D NMR spectroscopy on a benchtop NMR system accommodates diverse experimental requirements, from discrete time-point analysis to real-time reaction monitoring, while maintaining robust analytical performance across different chemical systems. The method's versatility in handling various reaction types and conditions underscores its potential as a standard analytical tool in synthetic chemistry.

[1] N. Peez, T. Rinesch, J. Kolz, W. Imhof; *Magnetic Resonance in Chemistry*; **2021**; *60.1,* 172-183. DOI: 10.1002/mrc.5210

[2] A. Slattery, Z. Wen, P. Tenblad, J. Sanjosé-Orduna, D. Pintossi, T. den Hartog, T. Noël, *Science,* **2024**, *383(6681)*. **DOI**: 10.1126/science.adj1817


isobutyraldehyde
p-phenylenediamine
40°C, CHCl3
- H2O
40°C, CHCl3
- H2O
XPhos Pd G2 (5 mol%)
K2CO3 (2.0 eq.)
2-MeTHF/H2O
r.t.
B(OH)3
KBr
EtOAc,
piperidine (cat.)
140°C, 7 bar,
10 min, 1mL/ min
Salicylic aldehyde
Ethyl acetoacetate
3-Acetyl coumarin
NMR tube
Reaction
52%
28%
20%
Spinsolve 80 ULTRA
Multi X