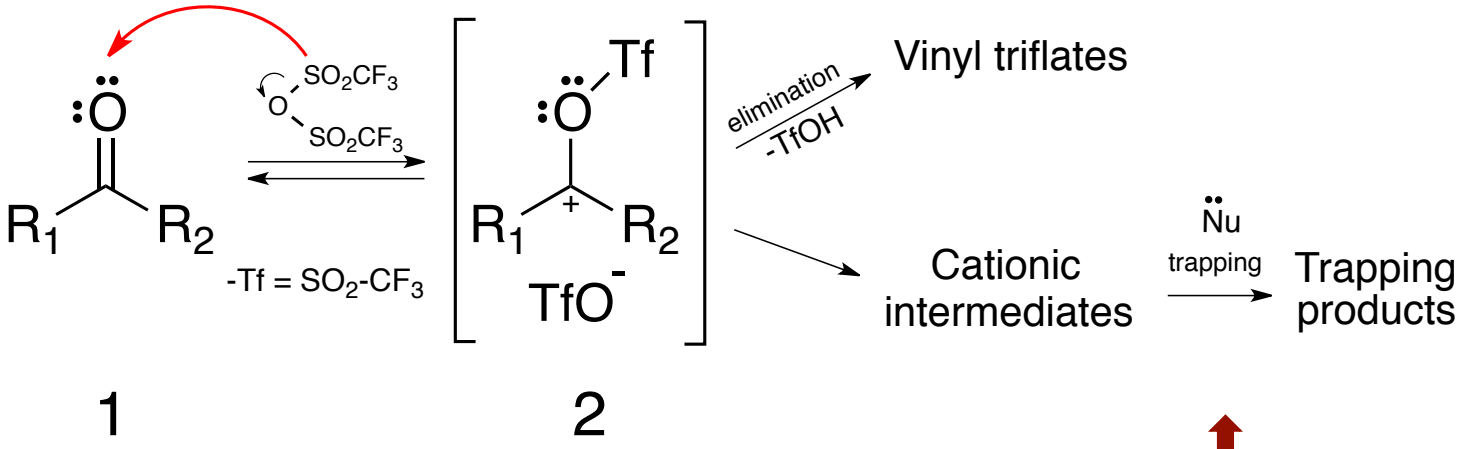
Small Molecule NMR Conference
September 22nd – 25th, 2013
Santiago de Compostela, Spain

Different attempts to monitor organic reactions in real time

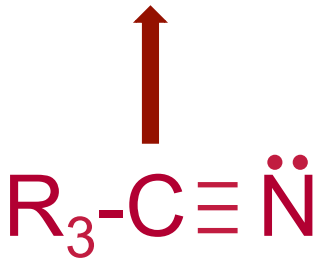
Encarnación Fernández-Valle, Antonio Herrera, Roberto Martínez-Álvarez, Dolores Molero
Zulay D. Pardo, Elena Sáez, Ángel Sánchez

Reaction of carbonyl compounds with electrophiles

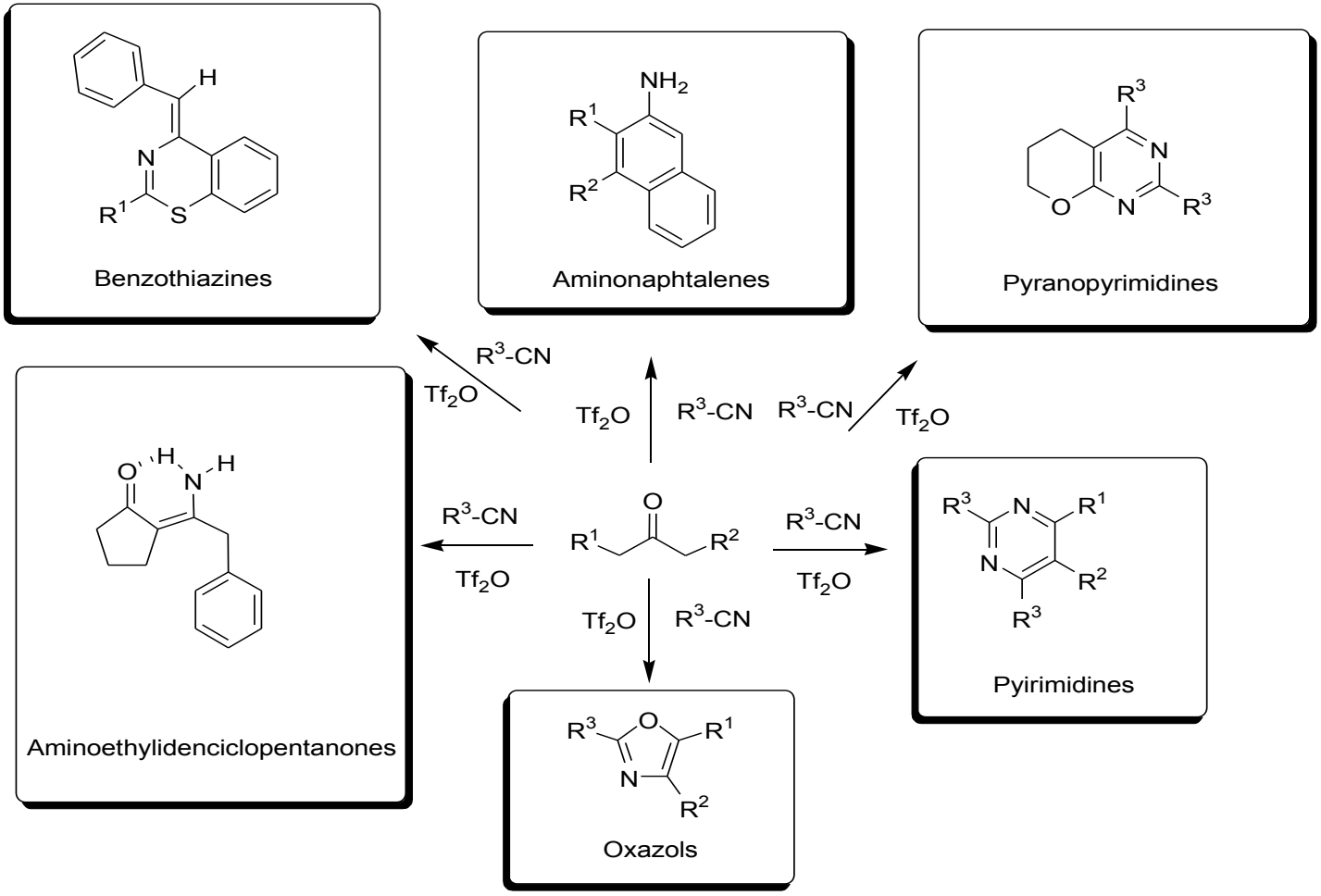


N-Heterocycles

- Benzothiazines
- Isochinolins
- Oxazols
- Pyrimidines
- etc.

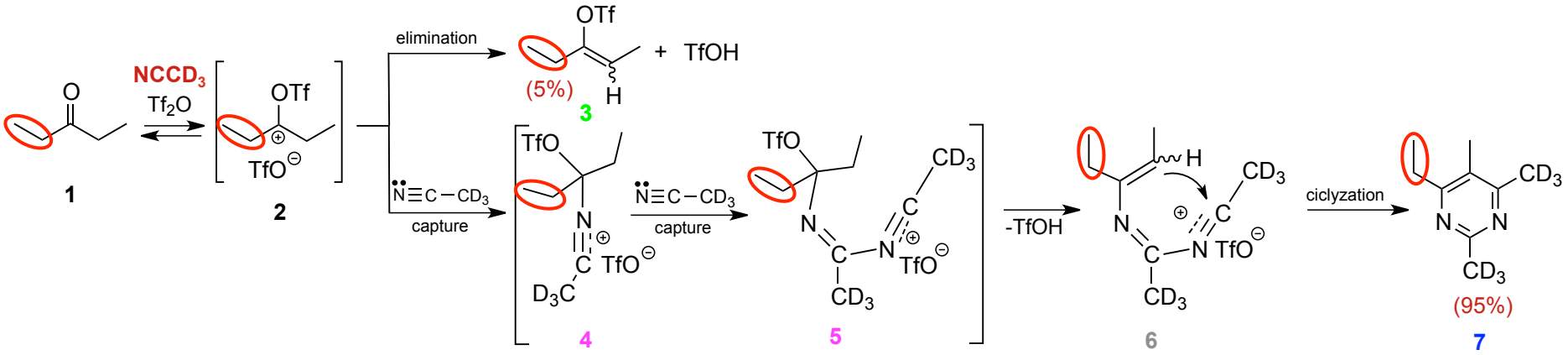


Synthesis of N-Heterocycles

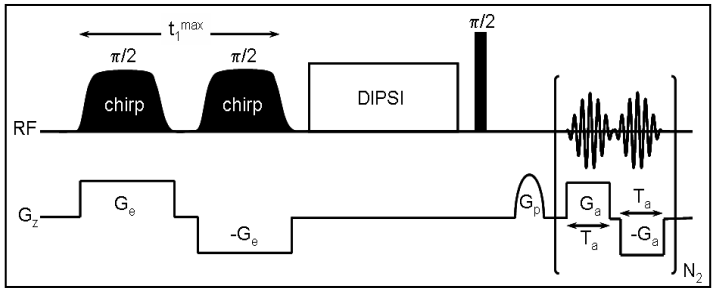


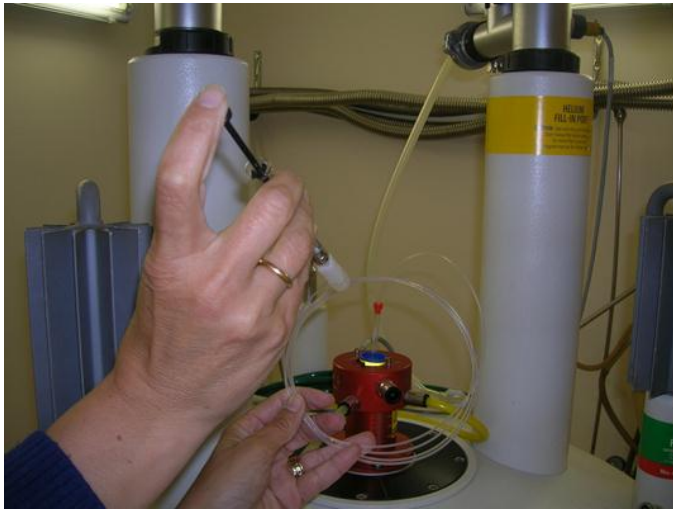
J. Org.Chem., **2006**, *71*, 3026-3032
Tetrahedron, **2009**, *65*, 1697–1703
Tetrahedron, **2009**, *65*, 5817–5823
Lett. Org. Chem., **2006**, *9*, 703-708
Eur. J. Org. Chem., **2006**, 3332-37
Monat. Chem., **2006**, *137*, 1421-1430

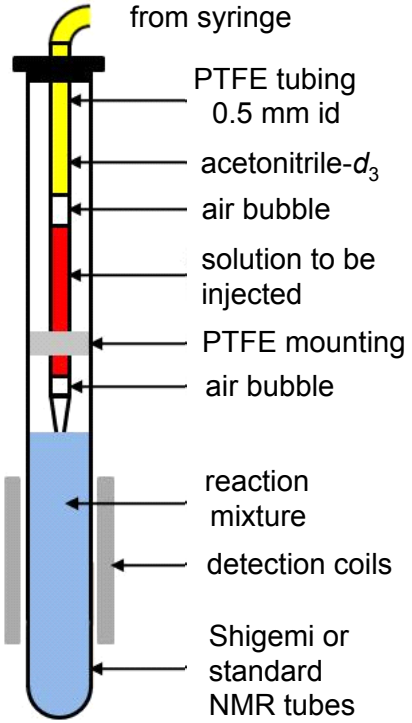
Monitoring organic reactions via UF-TOCSY



amp. mod. UF-TOCSY, 500 MHz







100 mM, 25C

Number of experiments = 525

Time between experiments = 10 s

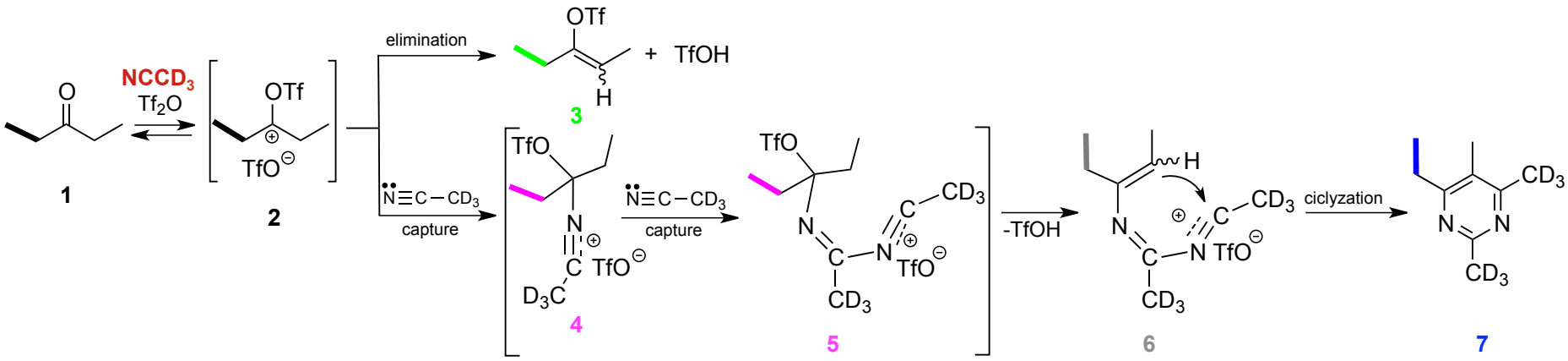
Time for each experiment = 0.135 s

Chirp pulses (60 kHz; Ge = 8 Gcm^{-1})

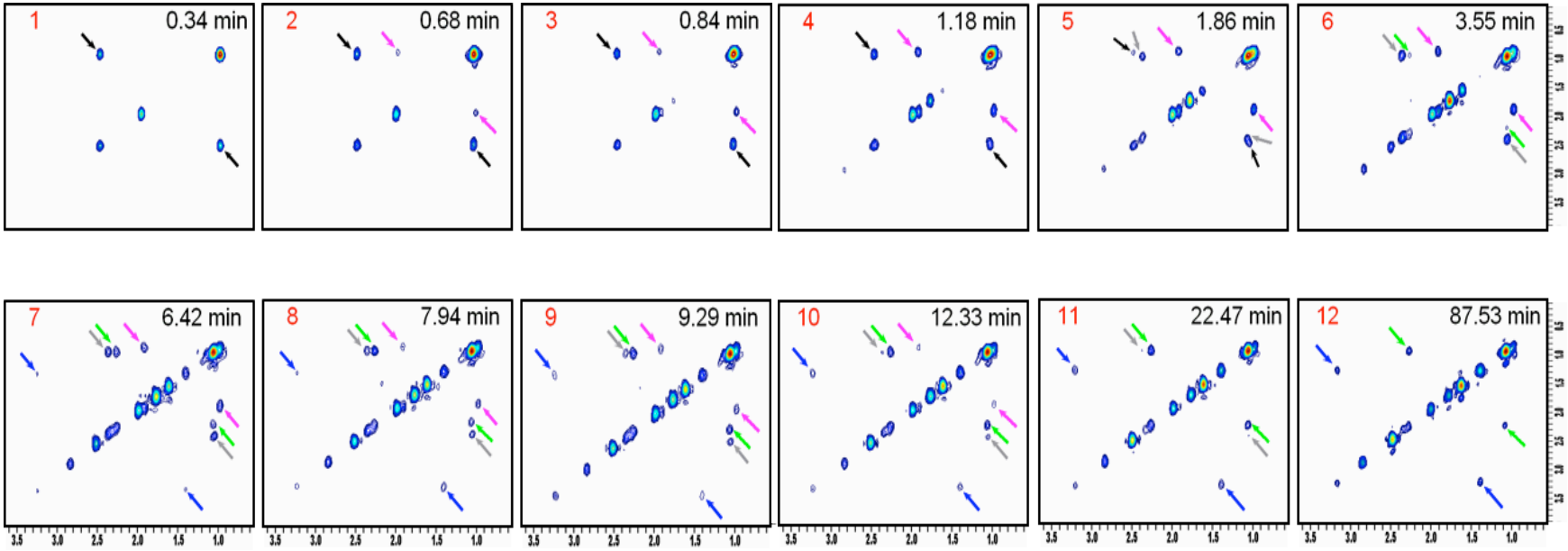
SW1 = 3.63 ppm; SW2 = 3.50 ppm

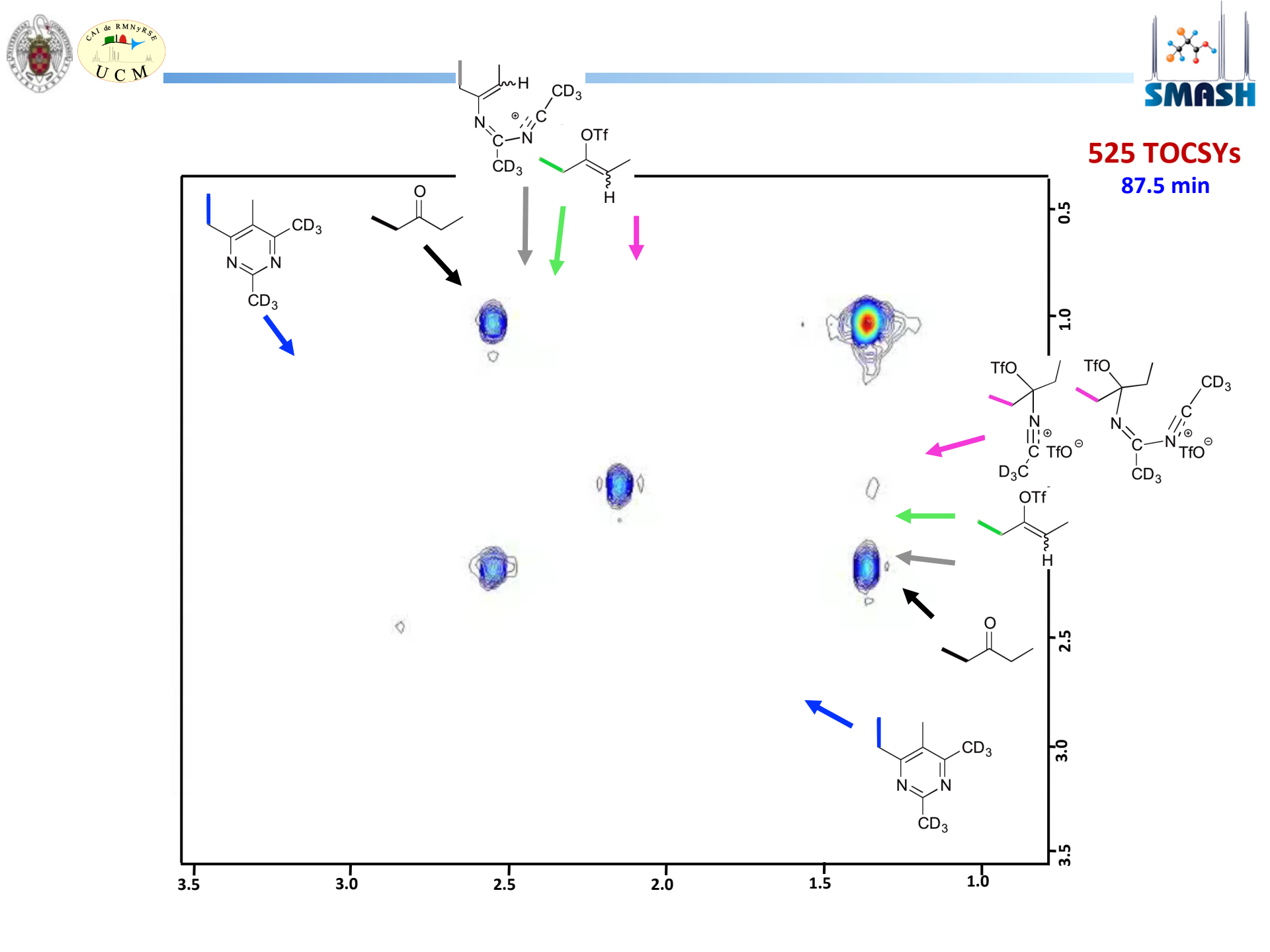
Time used for DIPSI = 20 ms

Monitoring organic reactions via UF-TOCSY

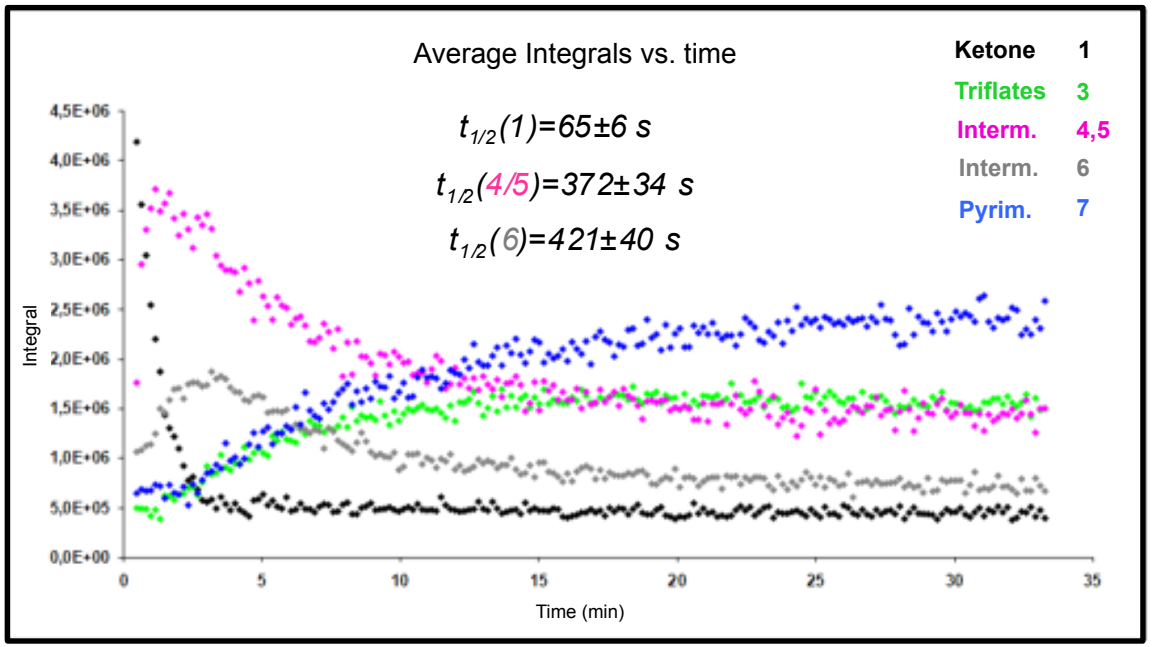


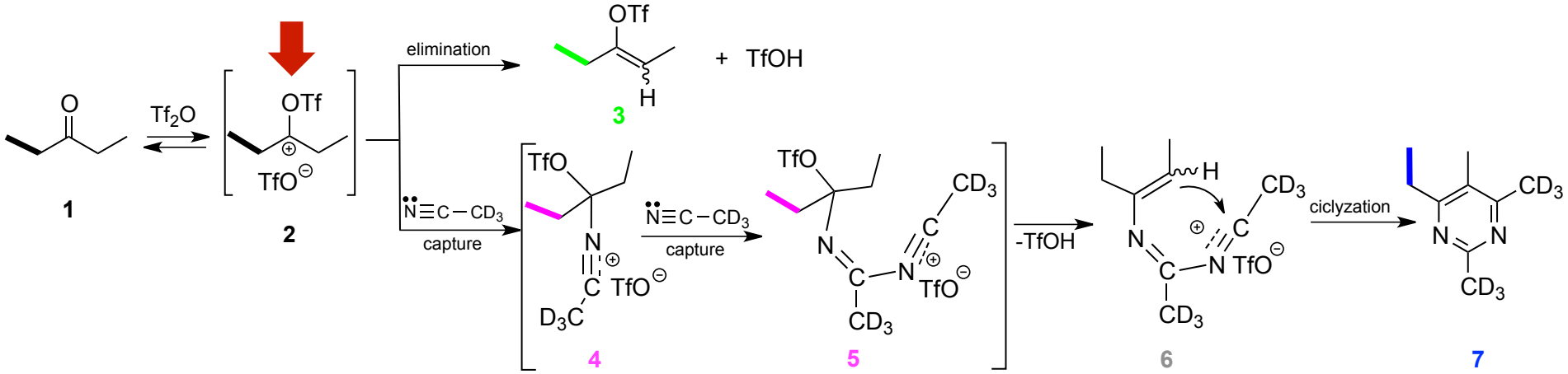
525 TOCSYs




525 TOCSYs
87.5 min
SMASH
CAI de RMNyRSE
UCM
CD3
OTf
TfO
D3C
0.5
1.0
2.5
3.0
3.5
1.5
2.0

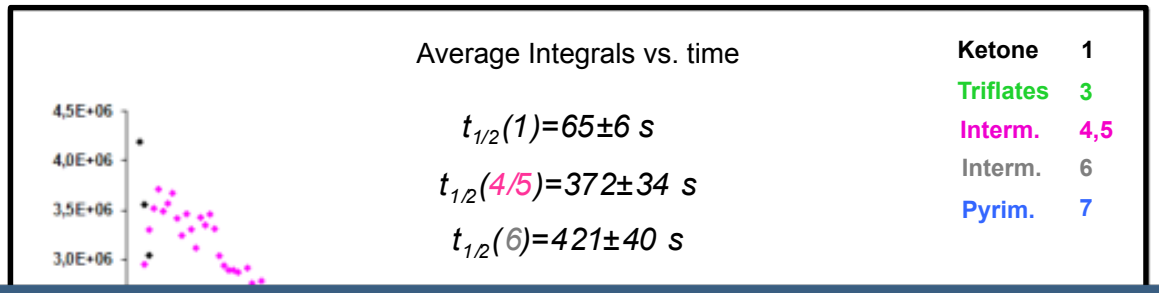
Real-time chemical processes monitoring via UF-TOCSY



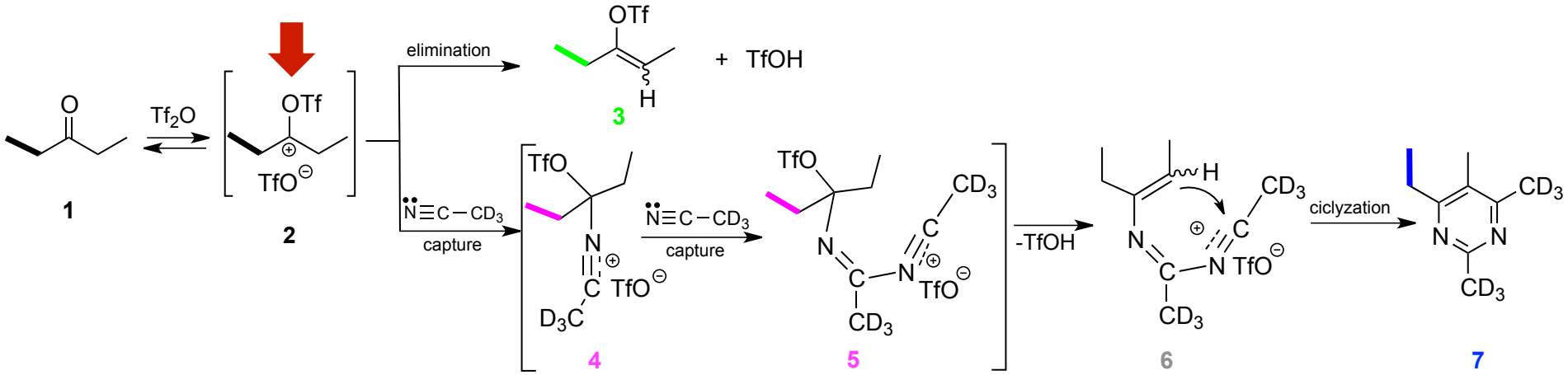


A. Herrera, E. Fernández-Valle, R. Martínez-Álvarez, D. Molero, Z. D. Pardo, E. Sáez, M. Gal. *Angew. Chem. Int. Ed.*, **2009**, *48*, 6274.

Real-time chemical processes monitoring via UF-TOCSY

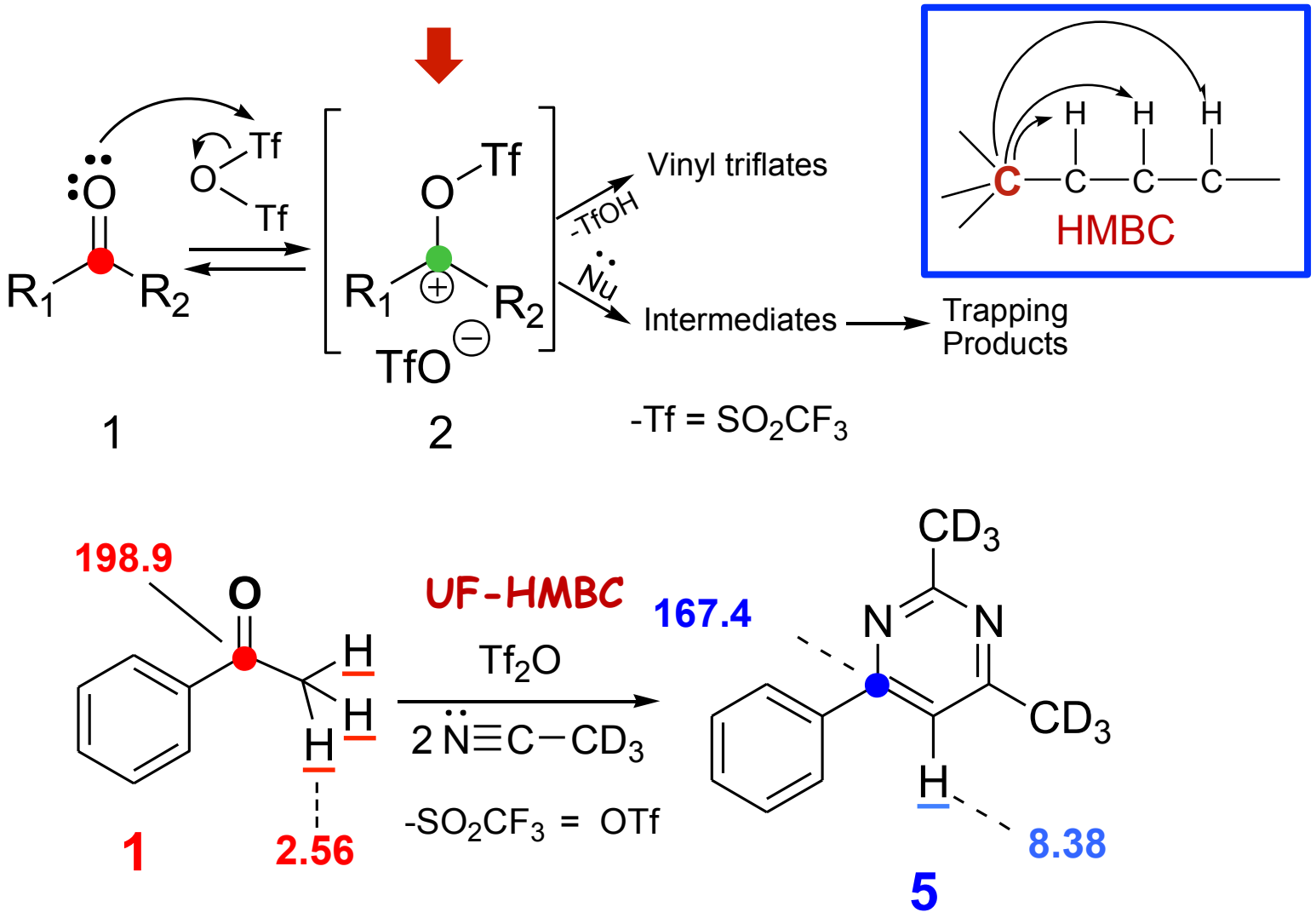


In summary, ***UF-TOCSY*** has permitted monitoring a multistep organic reaction in real time and provided spectroscopic evidence about the mechanism as well as kinetic data.

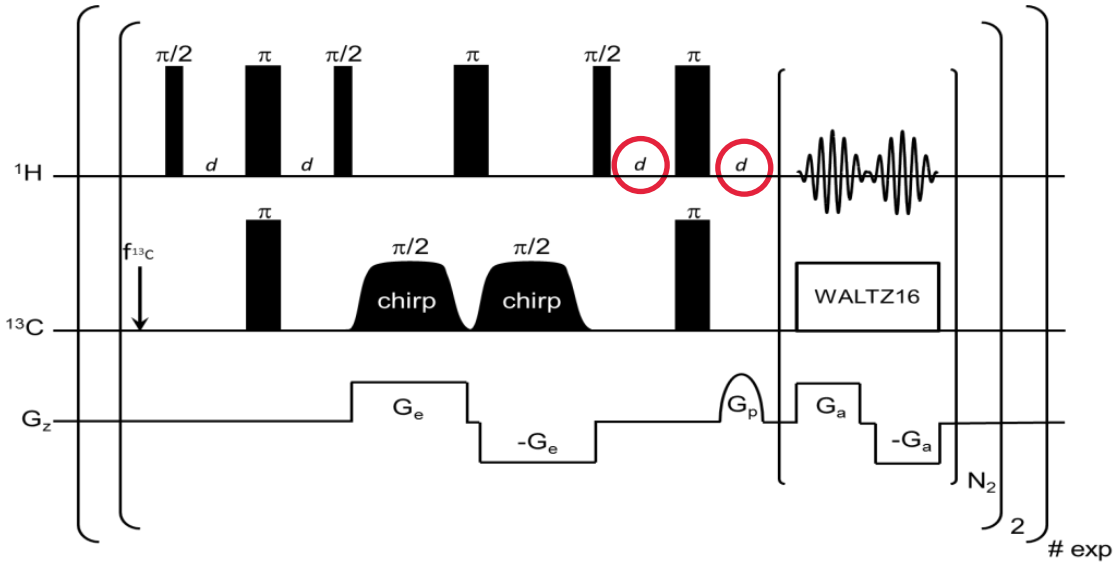


A. Herrera, E. Fernández-Valle, R. Martínez-Álvarez, D. Molero, Z. D. Pardo, E. Sáez, M. Gal. *Angew. Chem. Int. Ed.*, **2009**, *48*, 6274.

UF-HMBC as an efficient technique for monitoring quaternary carbons



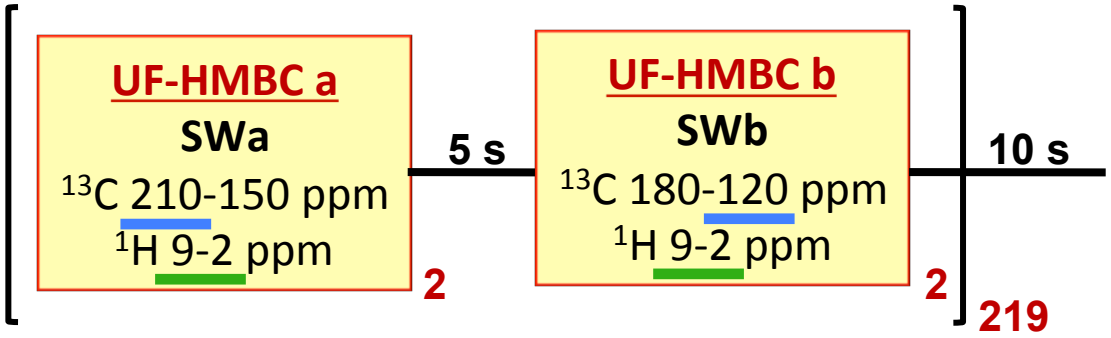
UF-HMBC as an efficient technique for monitoring quaternary carbons



500 MHz

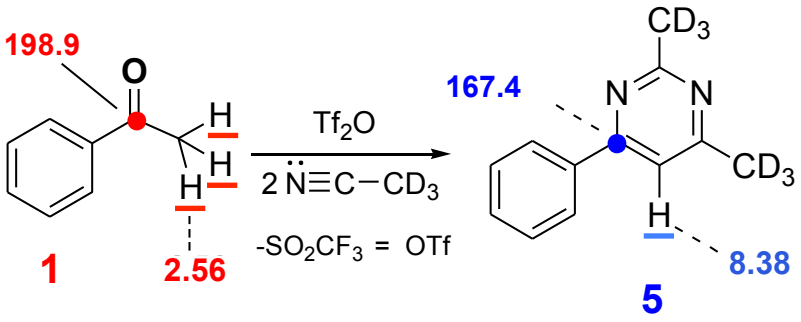
cont. esp.
encod. HSQC

d: 25 ms
$^{2}J,^{3}J \approx 10$ Hz



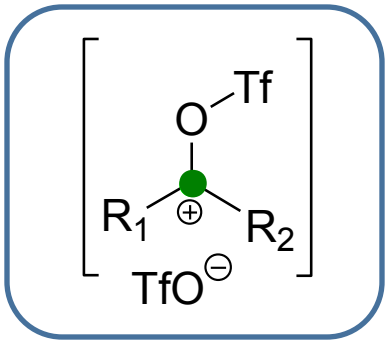
219*2 spectra
112.0 min
5.37 s/spectrum
10.0 s rep. time

Detection of intermediates by UF-HMBC

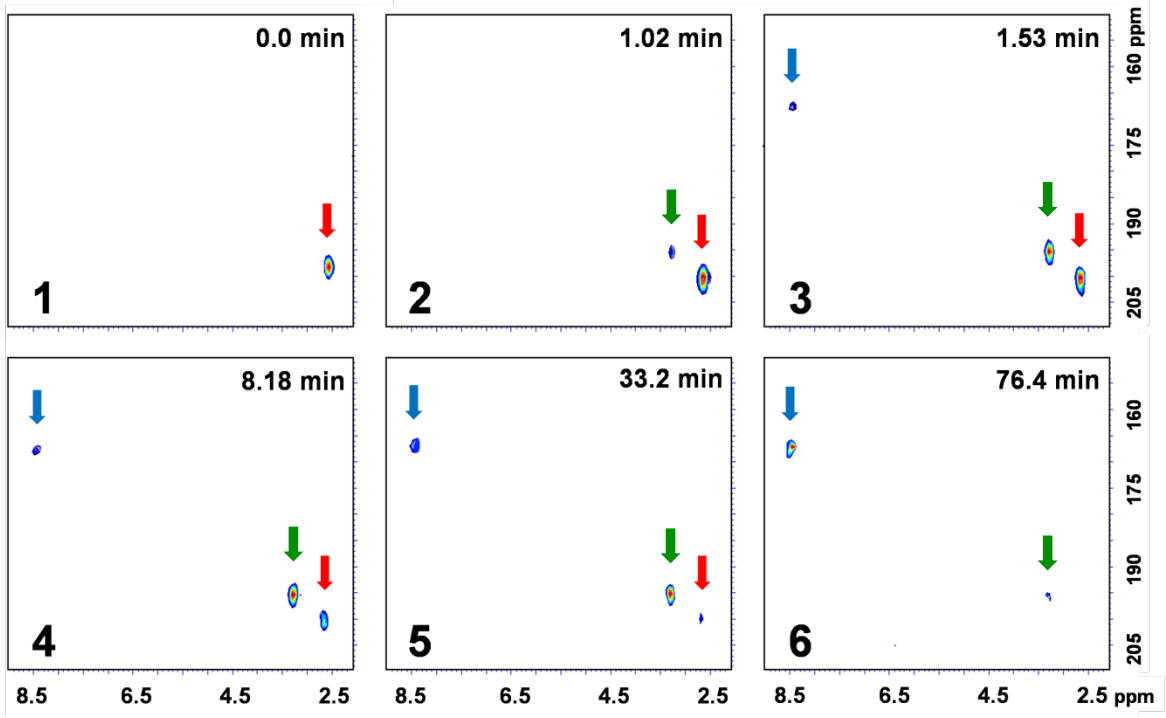


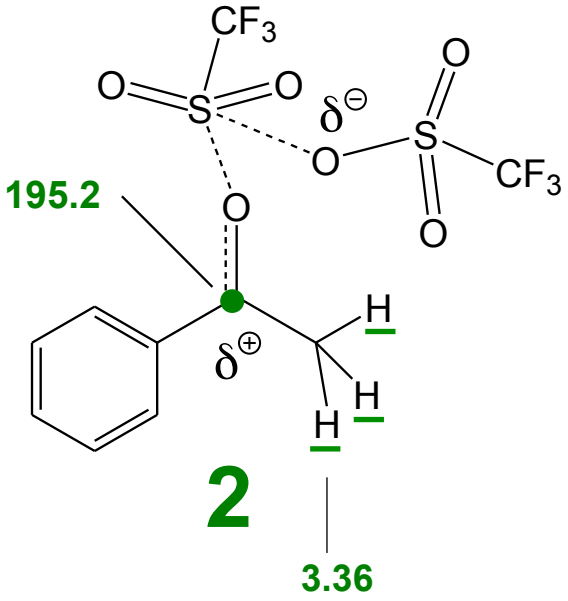
UF-HMBC a

^{13}C 210-150 ppm
^{1}H 9-2 ppm

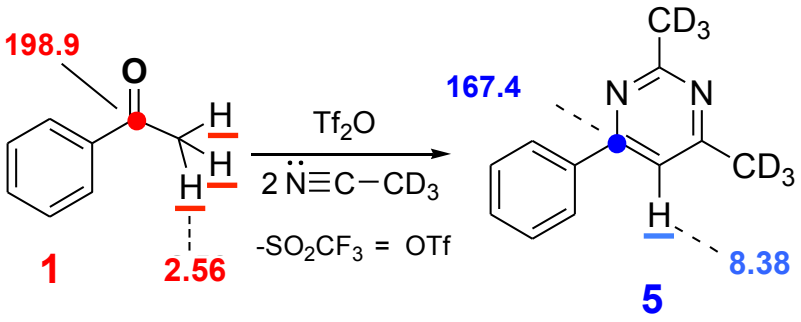


195.2 / 3.36 ppm





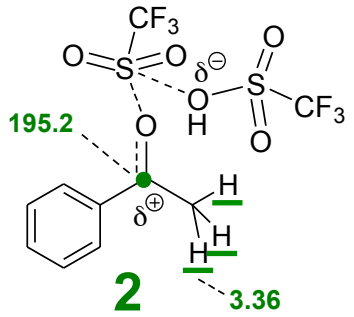
Detection of intermediates by UF-HMBC



UF-HMBC b

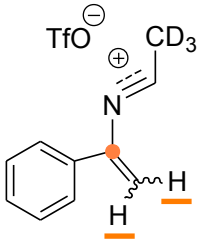
^{13}C 180-120 ppm

^{1}H 9-2 ppm

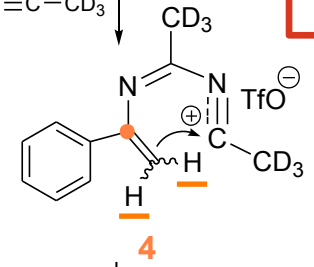


N≡C−CD_3

-TfOH



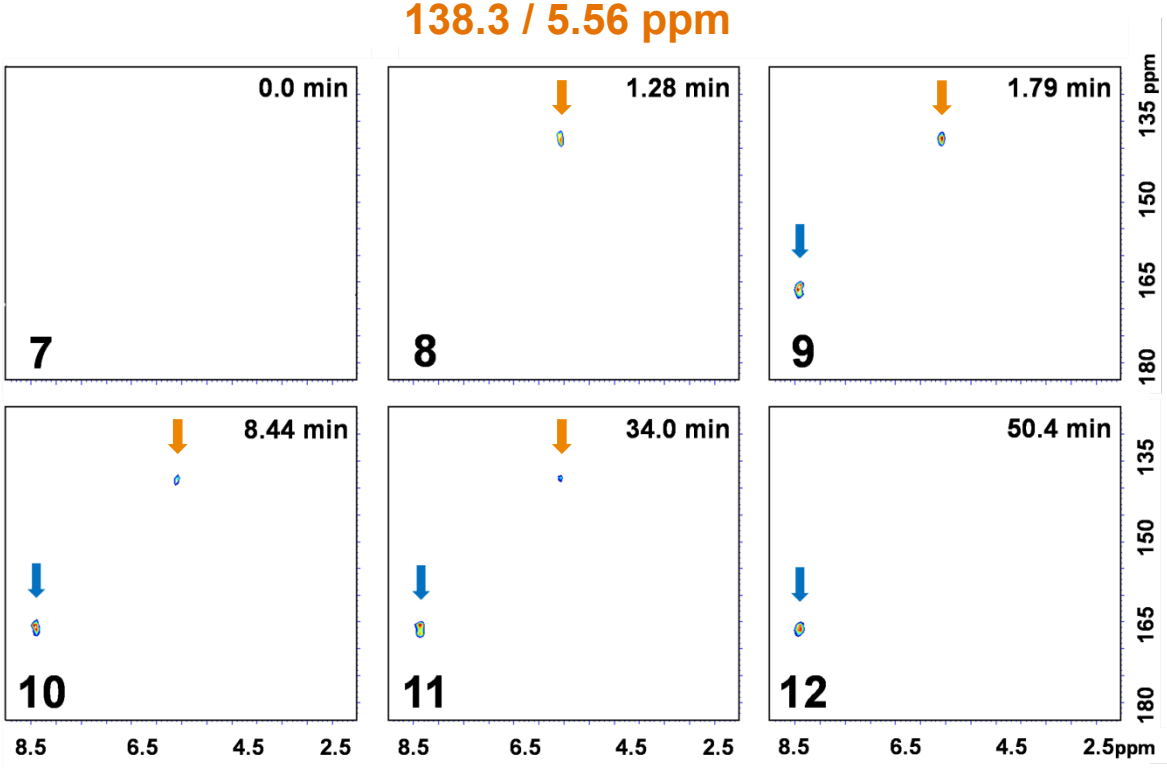
N≡C−CD_3



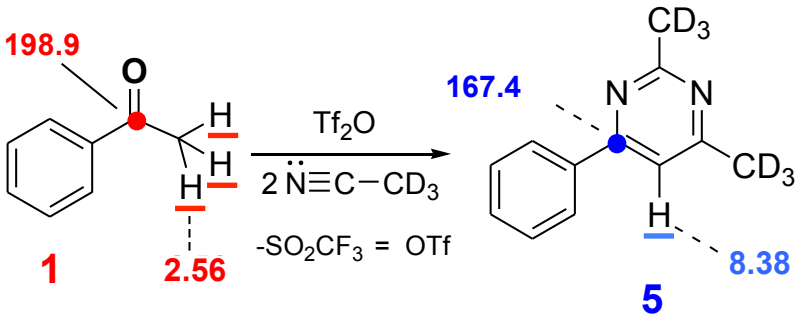
5

olefinic route

138.3 / 5.56 ppm



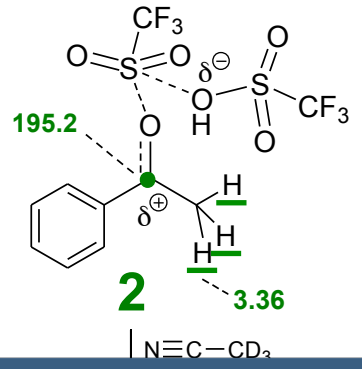
Detection of intermediates by UF-HMBC



UF-HMBC b

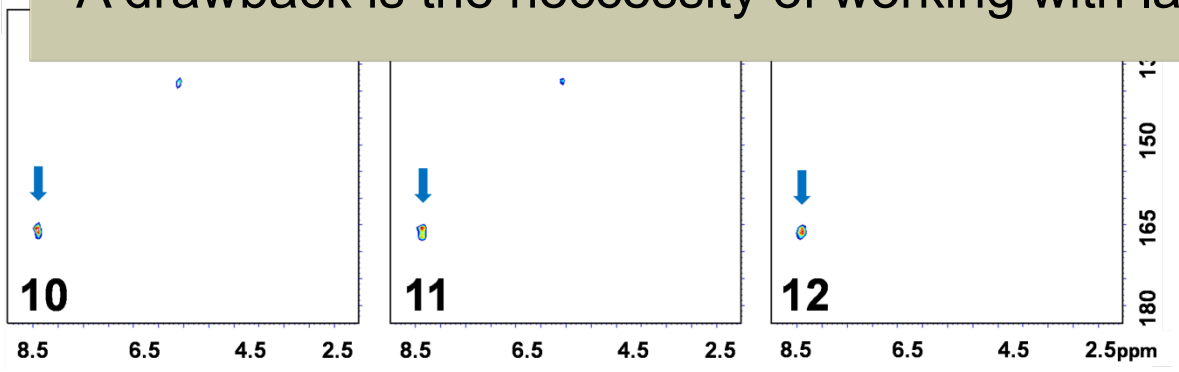
^{13}C 180-120 ppm

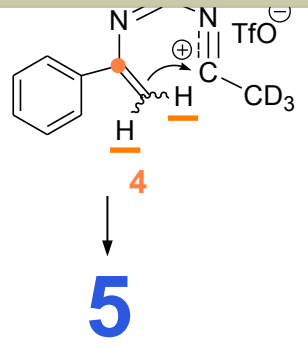
^{1}H 9-2 ppm



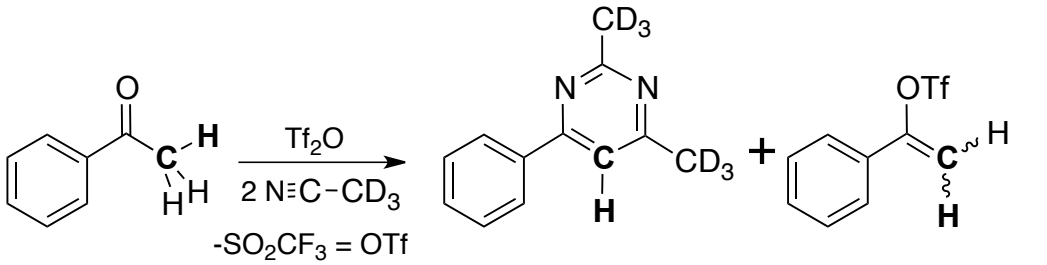
In summary, ***$^{1}H,^{13}C$ UF-HMBC*** has permitted real-time monitoring of a multistep reaction and provided new important mechanistic information and data (not shown here) about kinetic aspects.

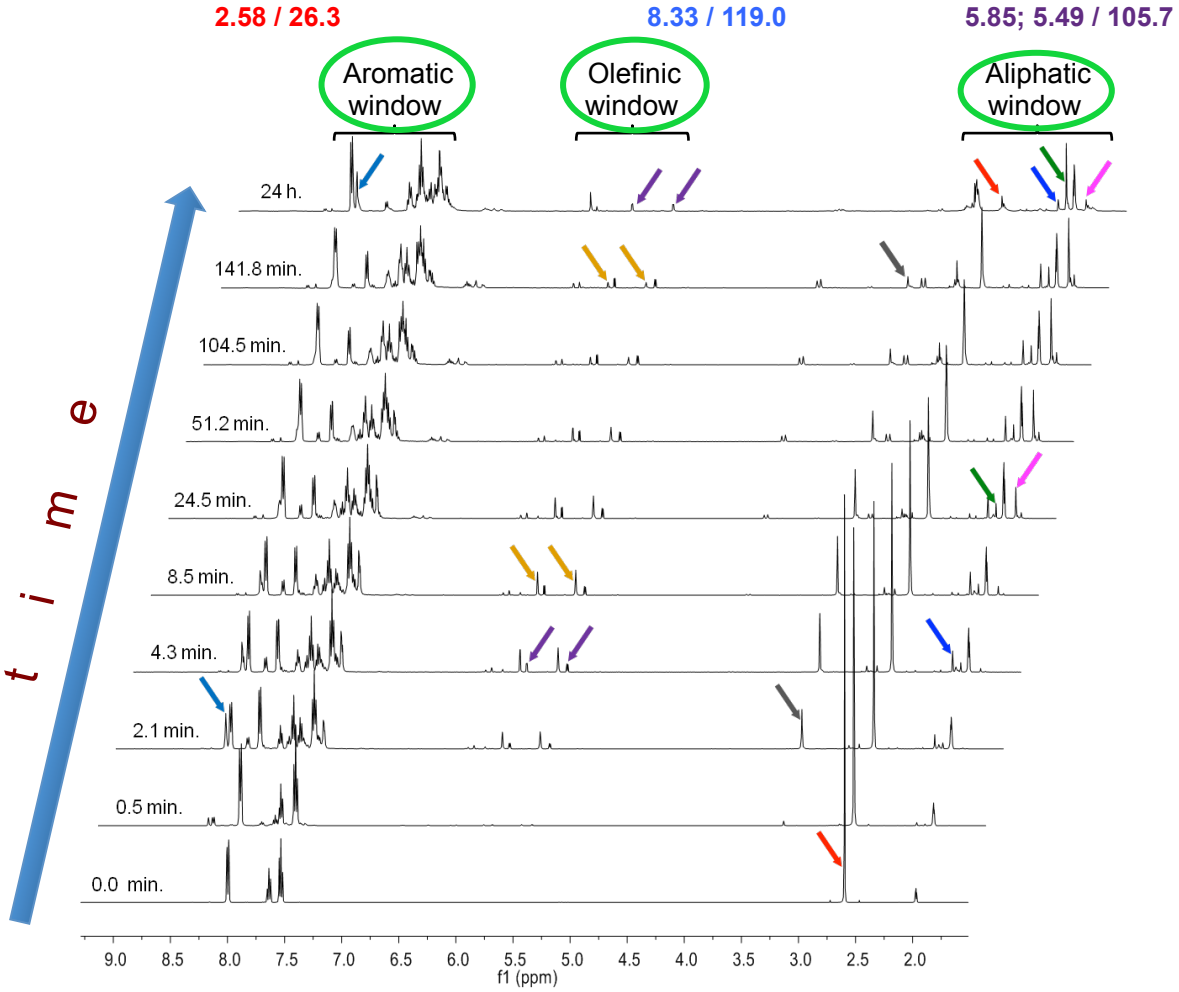
A drawback is the neccessity of working with labeled compounds.





Multiwindowed UF-HSQC

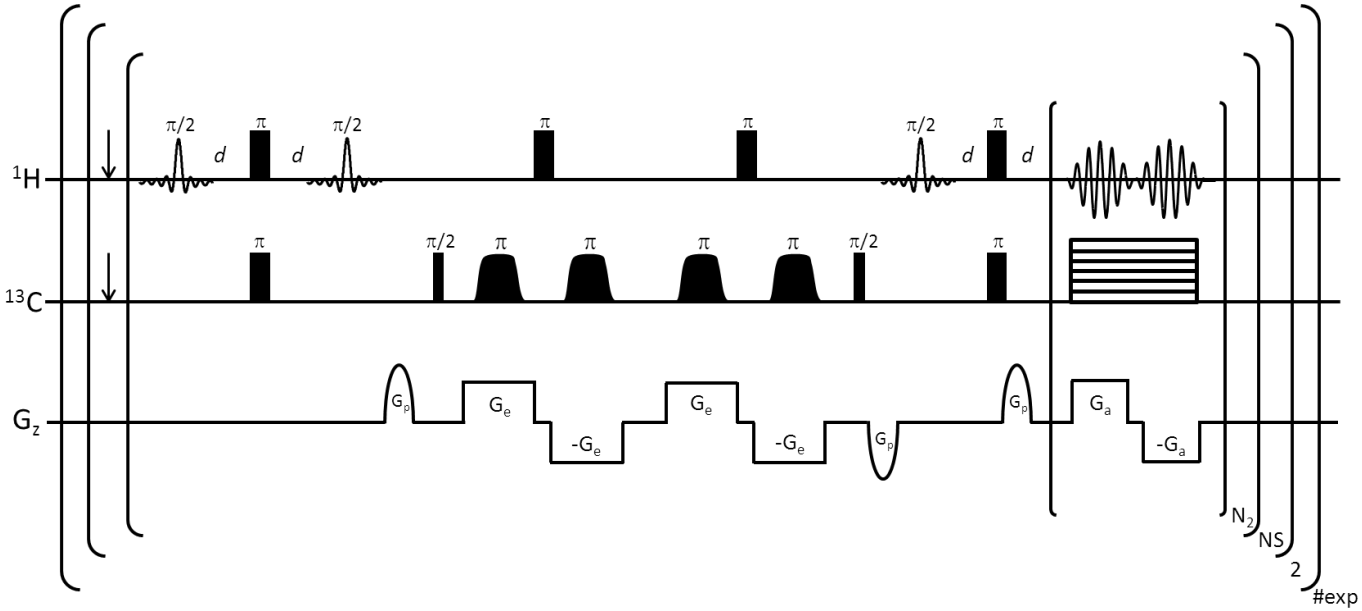




Multiwindowed UF-HSQC: pulse sequence

$\Delta\delta \approx$ **1.5 ppm** along the 1H dimension
$\Delta\delta \approx$ **10–20 ppm** along the 13C dimension

600 MHz

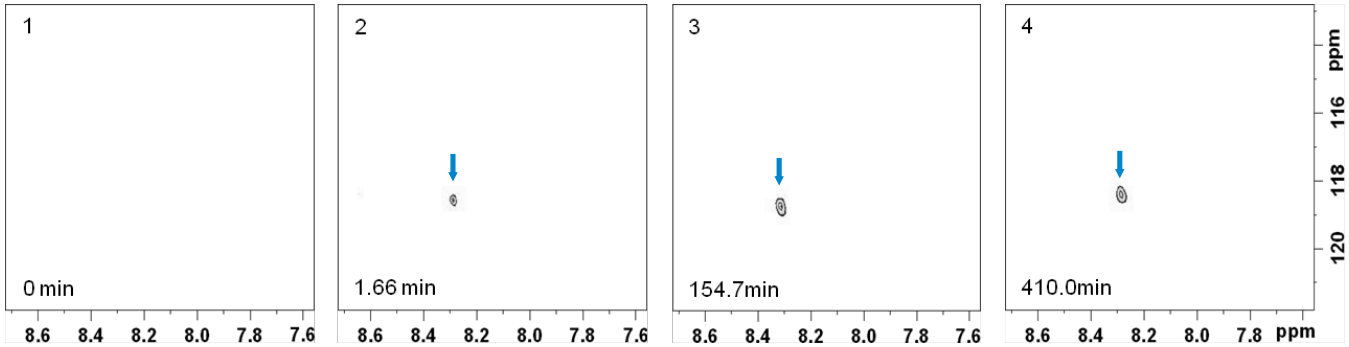


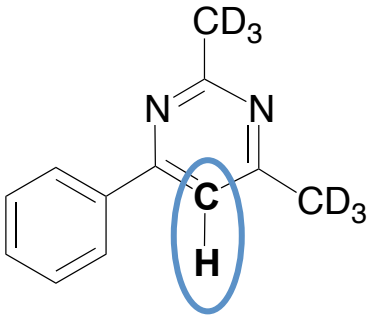
a) Selective excitation of protons in the targeted spectral windows (1.42 ms *sinc* π/2 pulses).
b) Spatial encoding with 2.5 ms π chirp pulses. Encoding gradient strengths: 25 G/cm.
c) Four chirped pulses applied in the presence of suitable gradients.
d) $(\pi)^H$ decoupling pulses to give a constant-time spatial encoding of the carbon evolution.
e) An INEPT magnetization transfer to carbon.
f) Read-out of encoded signals typically used N_2 = 40 cycles and a G_a of 6.35 or 10.6 G/cm.

Multiwindowed UF-HSQC: aromatic window

Δ 7.49−8.81 ppm for 1H and 112.40−122.40 ppm for 13C

8.33 / 119.0 ppm

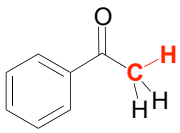




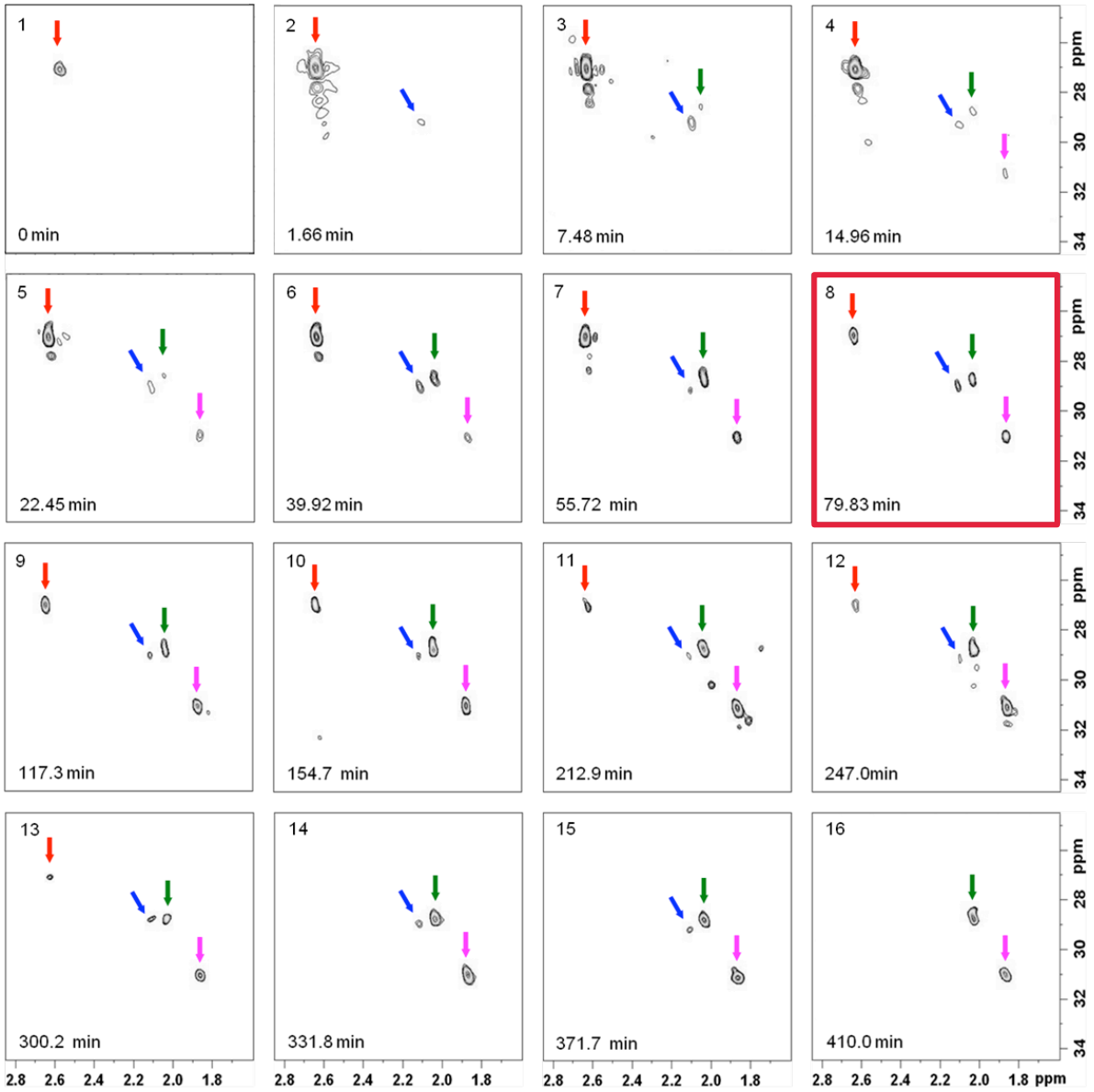
8.33 / 119.0

Multiwindowed UF-HSQC: aliphatic window

Δ 1.54−2.87 ppm for 1H with 23.7−33.7 ppm for 13C



2.58 / 26.3 ppm



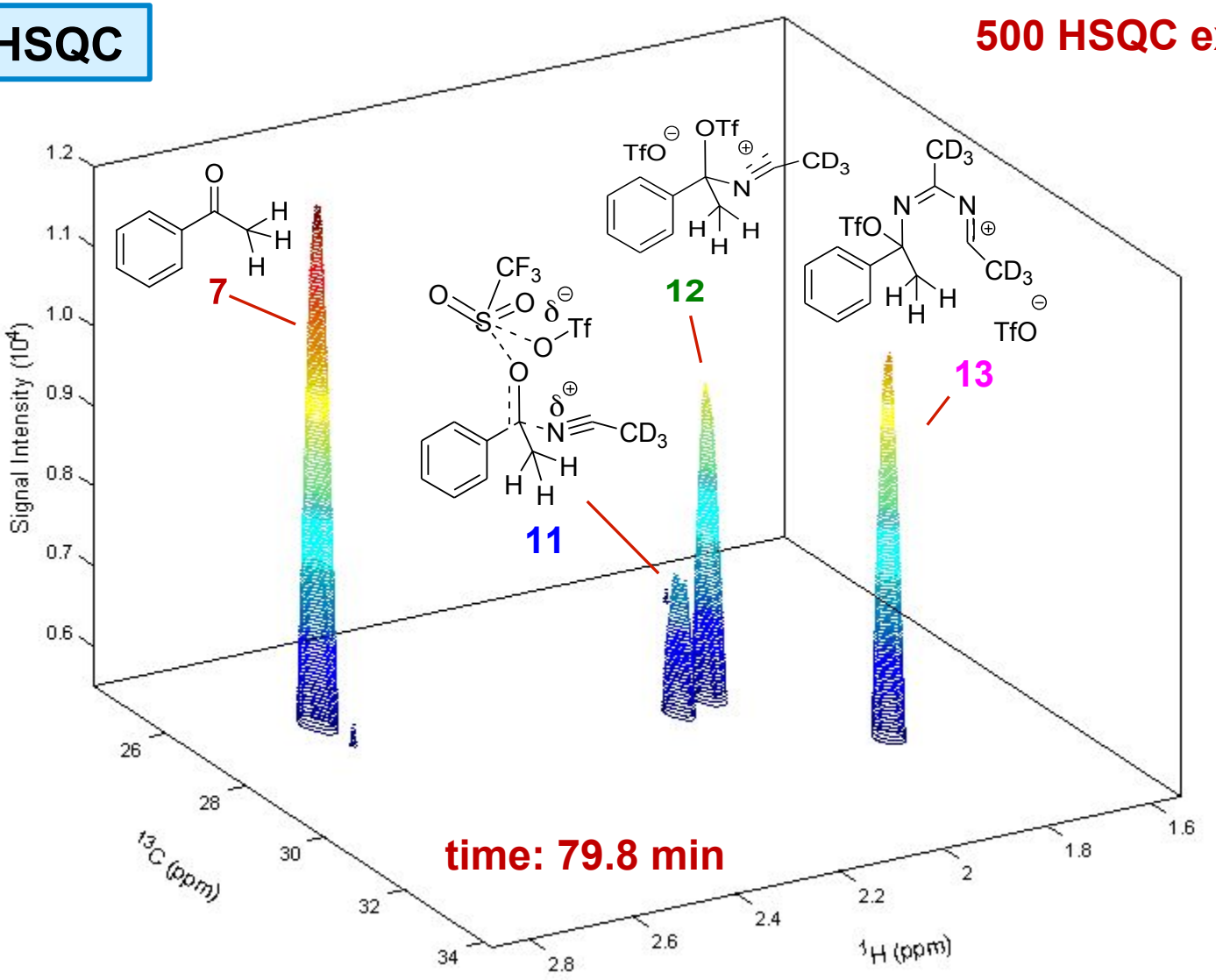
500 HSQC experiments

Multiwindowed UF-HSQC: aliphatic window

Δ 1.54 – 2.87 ppm for 1H with 23.7 – 33.7 ppm for 13C

UF-HSQC

500 HSQC experiments



Zulay D. Pardo, Gregory L. Olsen, E. Fernández-Valle, L. Frydman, R. Martínez-Álvarez, A. Herrera. *J. Am Chem. Soc.*, 2012, *134*, 2706-2715.

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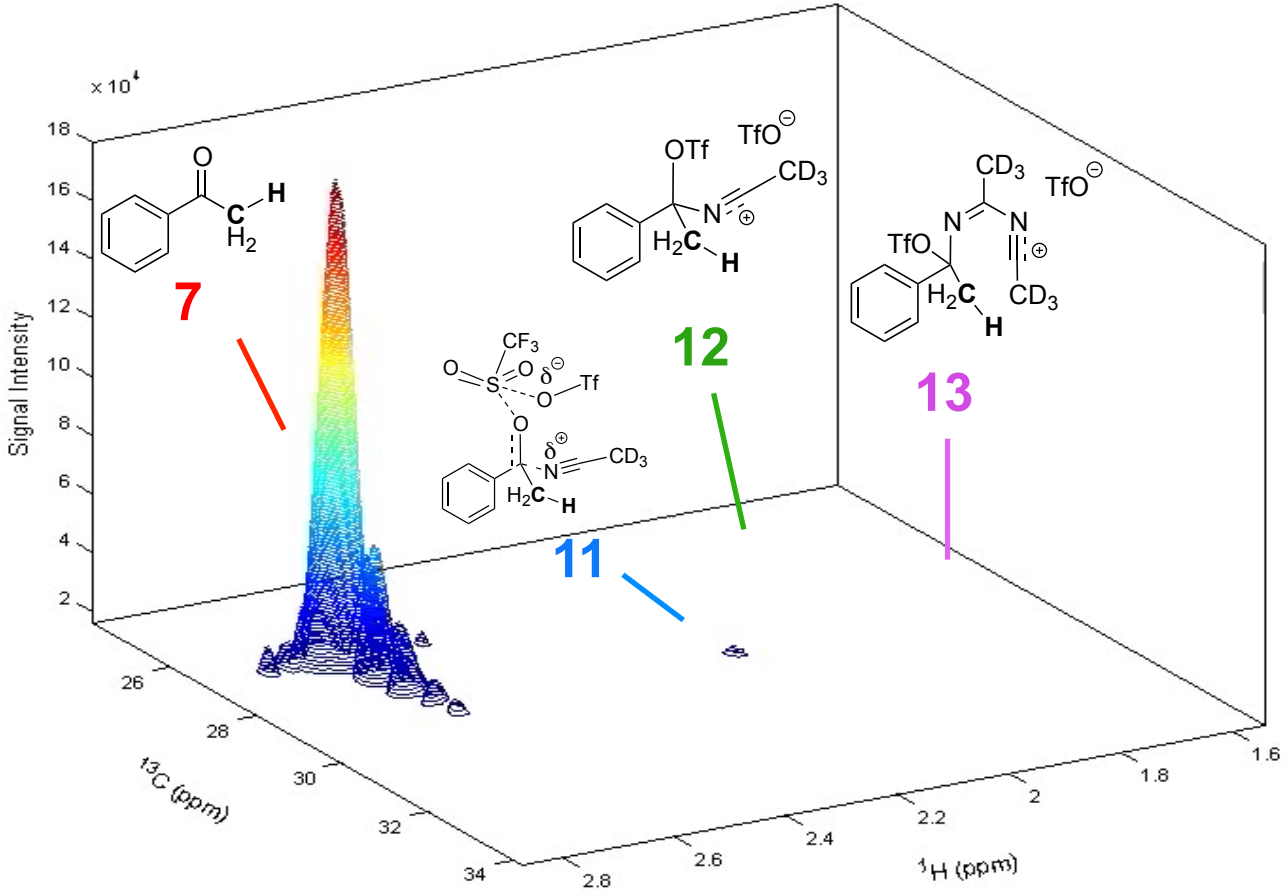
Δ 1.54 – 2.87 ppm for 1H with 23.7 – 33.7 ppm for 13C



Multiwindowed UF-HSQC: aliphatic window

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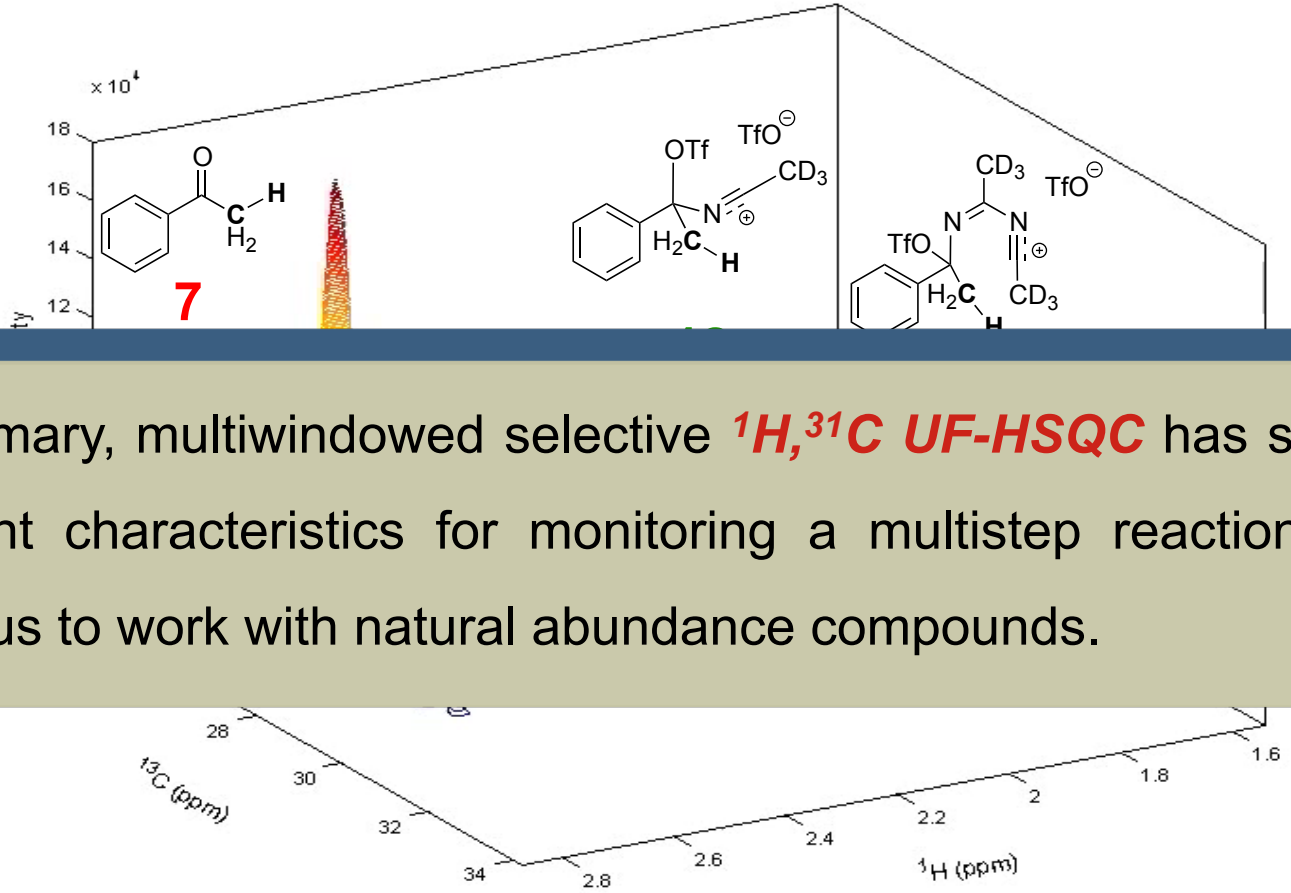
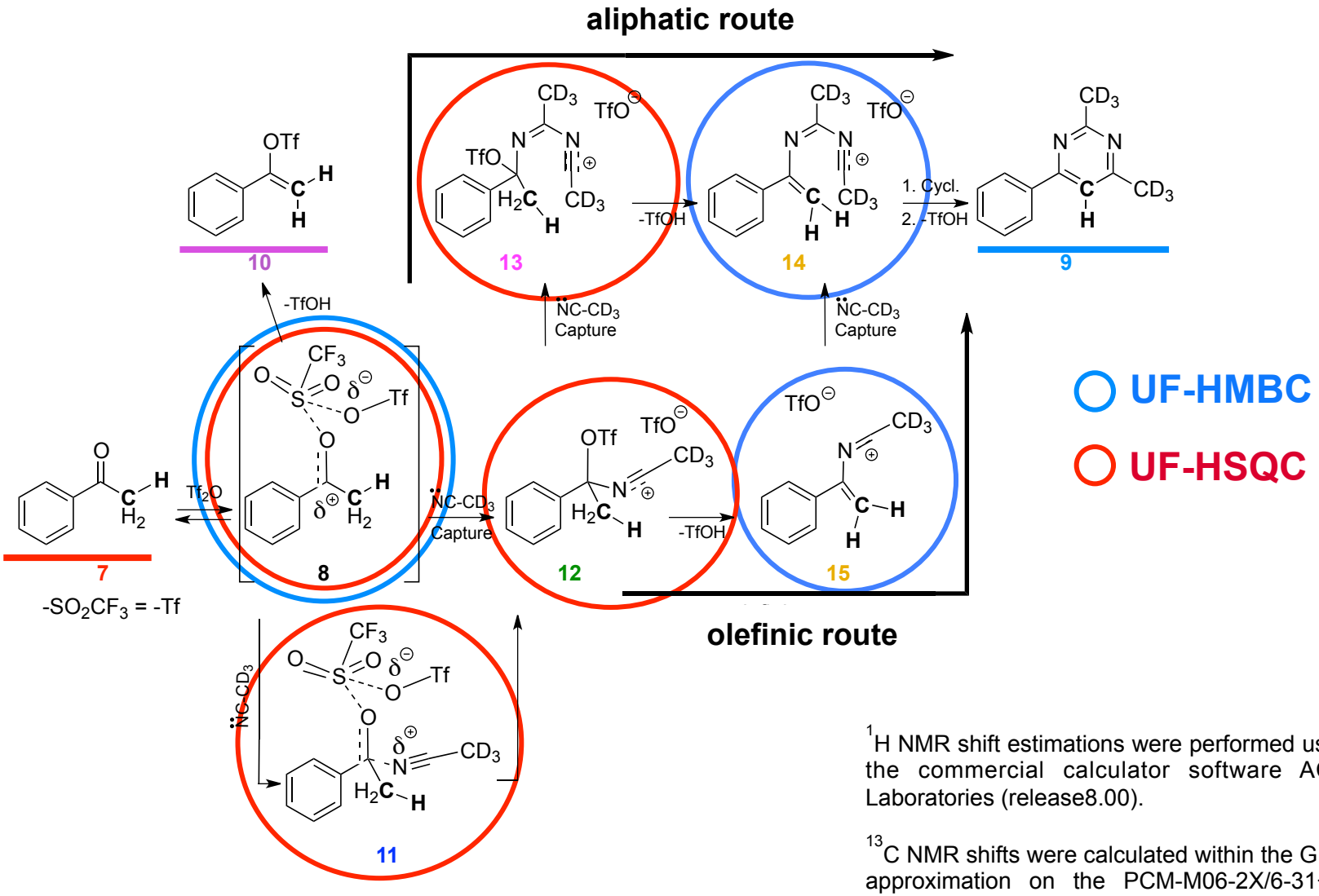


In summary, multiwindowed selective ***$^{1}H,^{31}C$ UF-HSQC*** has shown excellent characteristics for monitoring a multistep reaction and allows us to work with natural abundance compounds.

Mechanism after UF-HSQC



UF-HMBC

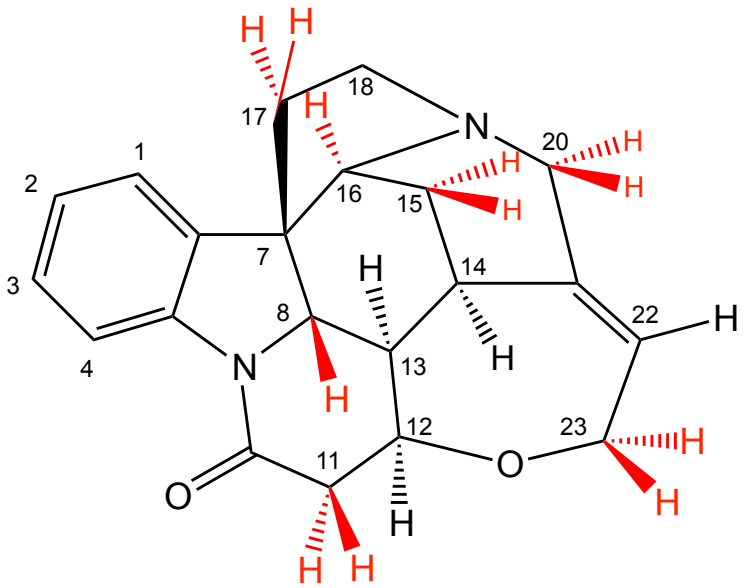
UF-HSQC

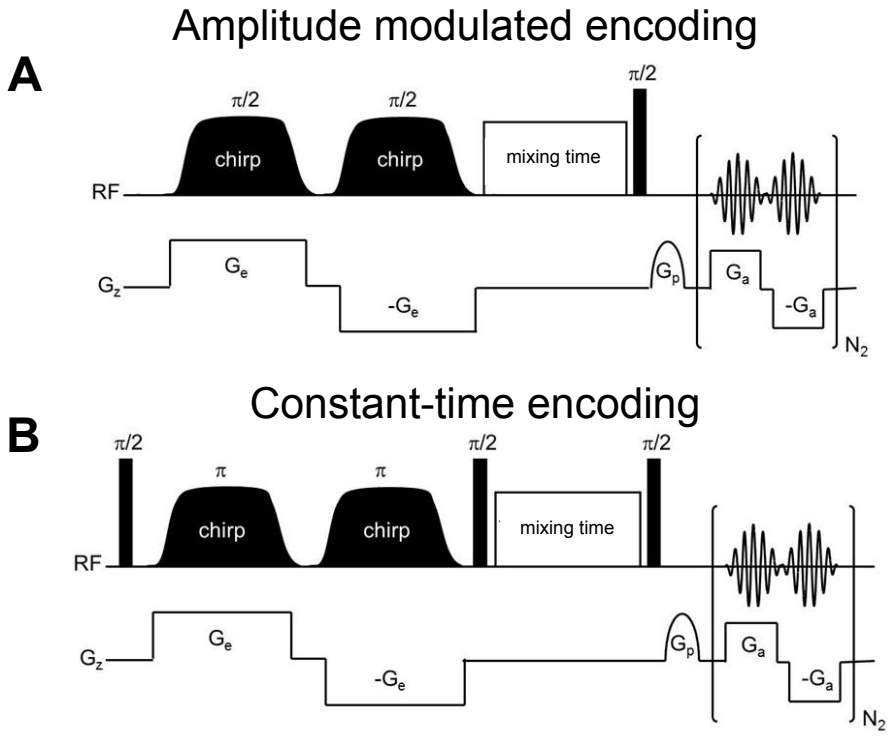
^{1}H NMR shift estimations were performed using the commercial calculator software ACD/ Laboratories (release8.00).

^{13}C NMR shifts were calculated within the GIAO approximation on the PCM-M06-2X/6-31+G* (solvent=acetonitrile) with optimized geometries using the Gaussian09 suite of programs.

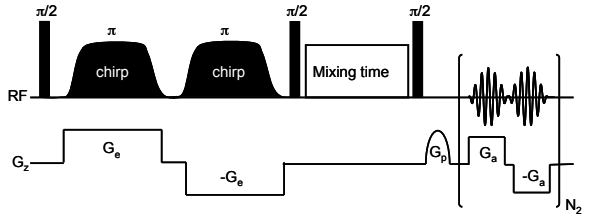
Zulay D. Pardo, Gregory L. Olsen, E. Fernández-Valle, L. Frydman, R. Martínez-Álvarez, A. Herrera. *J. Am Chem. Soc.*, 2012, *134*, 2706-2715.

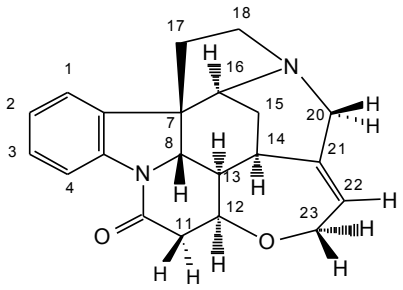
Detection of dipolar interaction by UF-NOESY

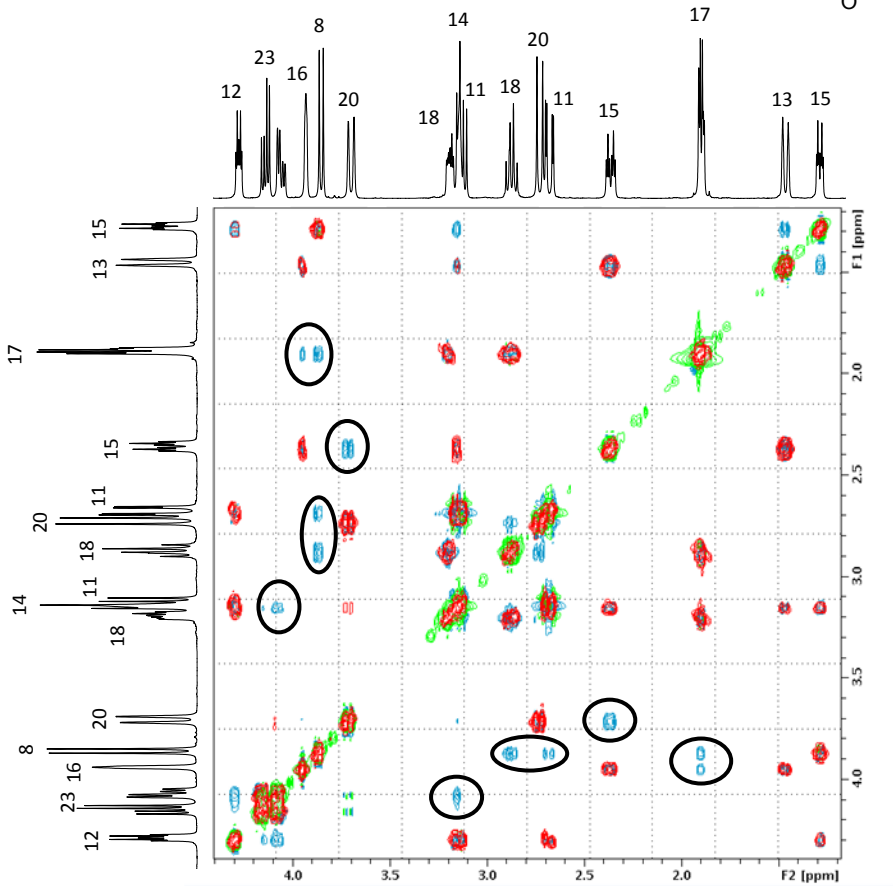


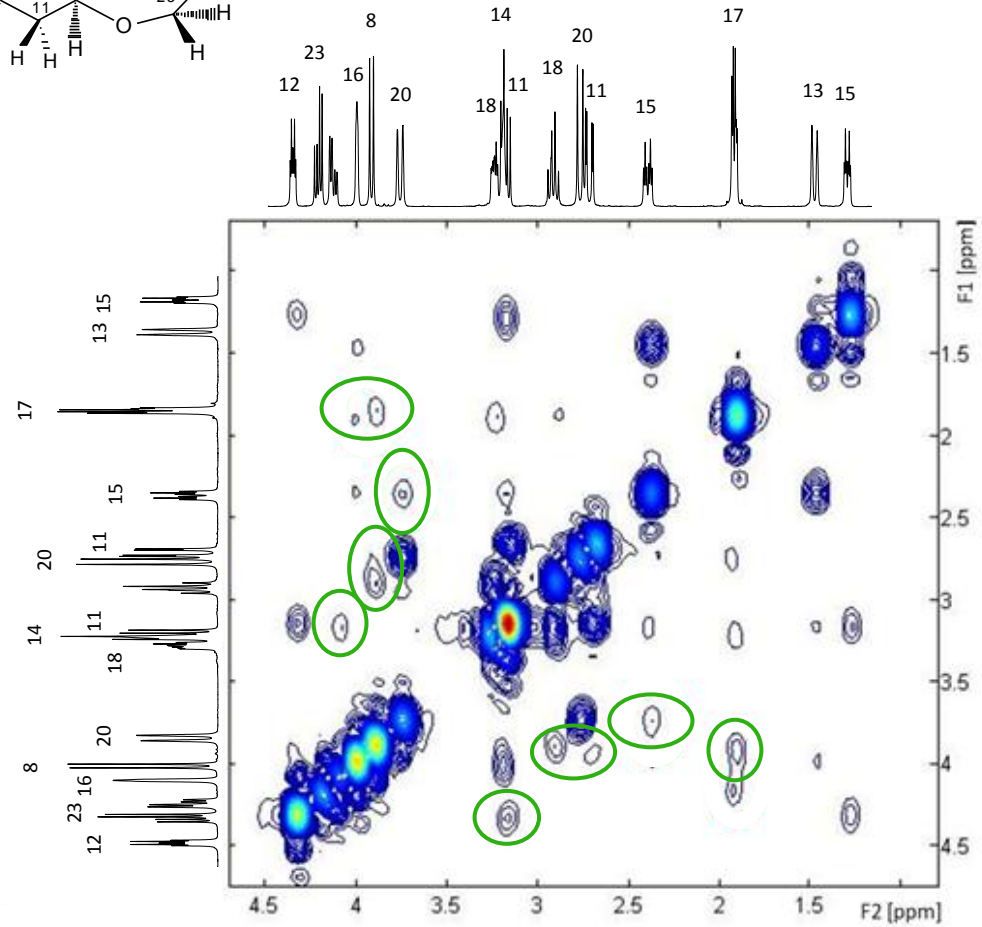


Detection of dipolar interaction by UF-NOESY







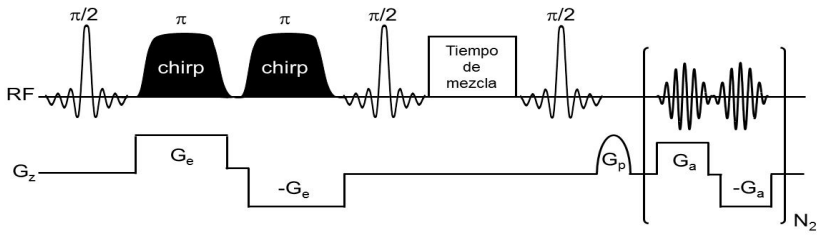


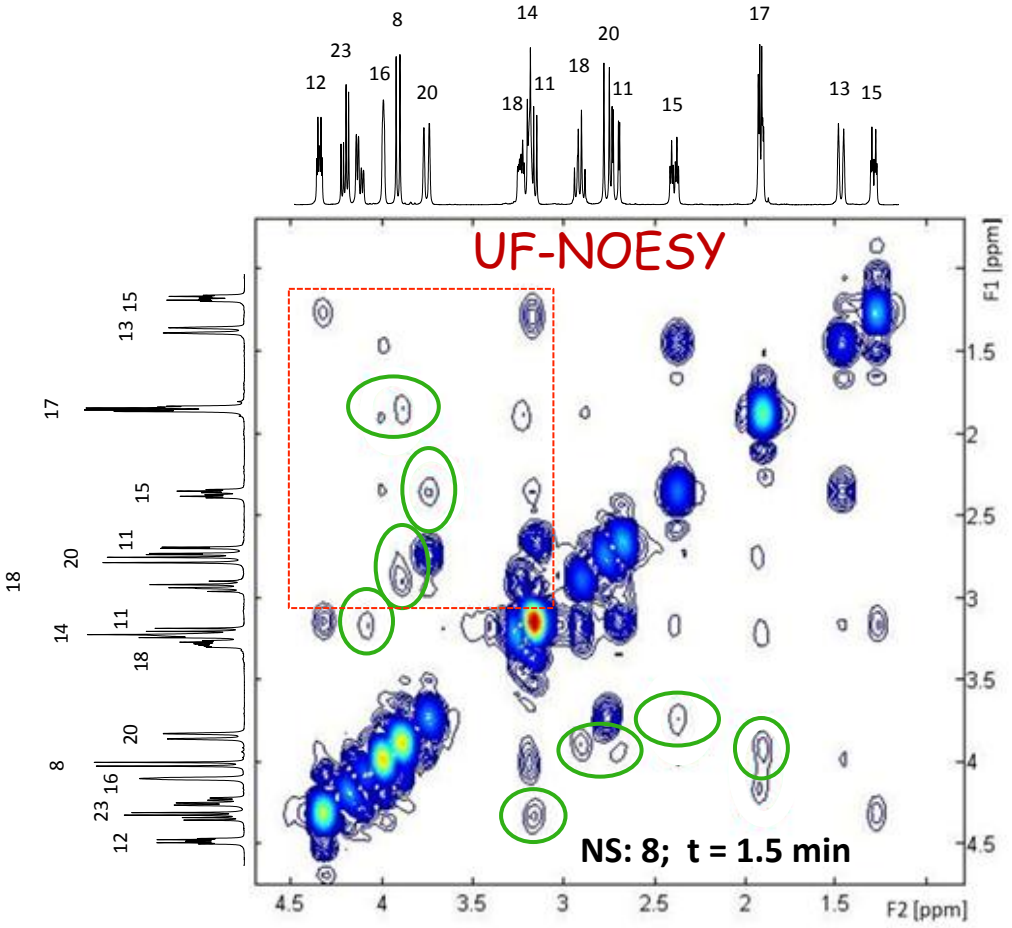
NOESY-TOCSY / 500 MHz / 100 mM
t = 1 h

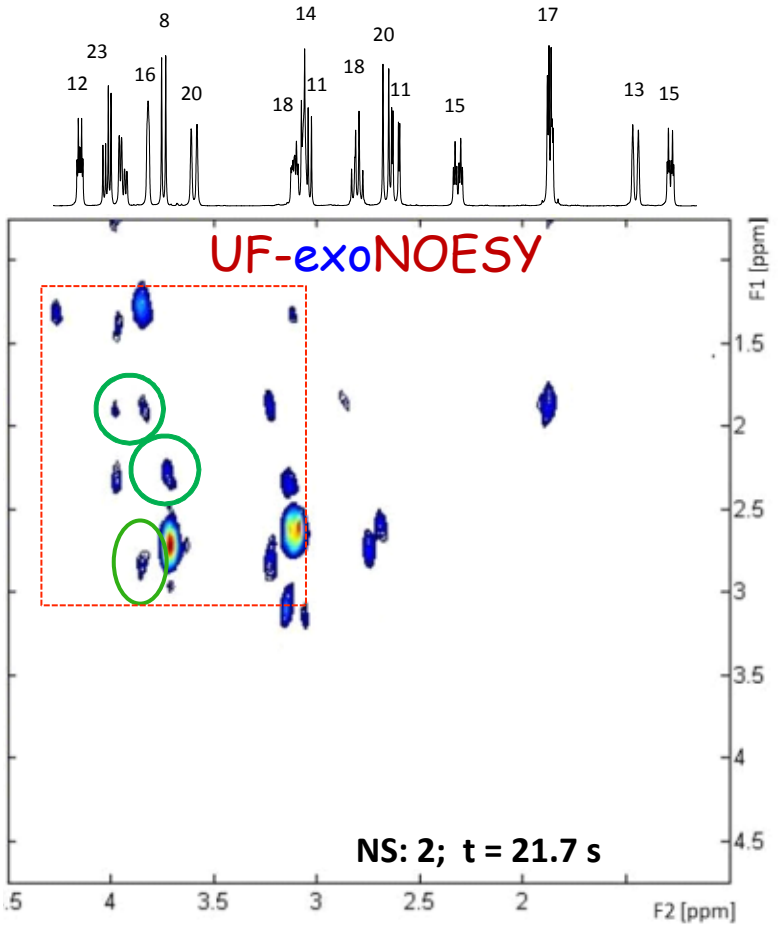
UF-NOESY / 500 MHz / 300 mM
NS: 8; t = 1 min 29 s

○ Unambiguous signals produced by NOE

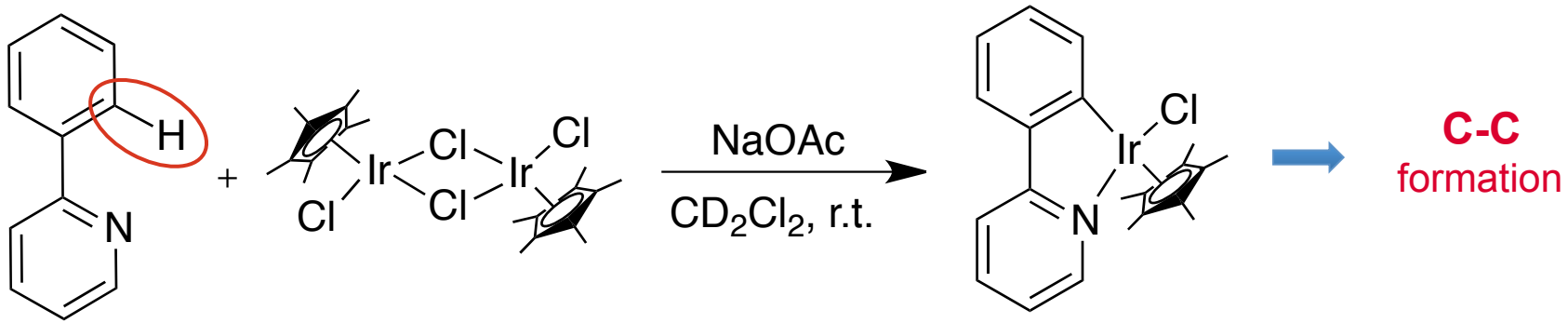
UF-exoNOESY


π/2
π
chirp
π
chirp
π/2
Tiempo de mezcla
π/2
RF
G_z
G_e
$-G_e$
G_p
G_a
$-G_a$
N_2

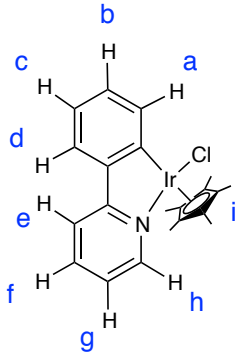

UF-NOESY
NS: 8; t = 1.5 min
F1 [ppm]
F2 [ppm]


UF-exoNOESY
NS: 2; t = 21.7 s
F1 [ppm]
F2 [ppm]

Testing organometallic compounds



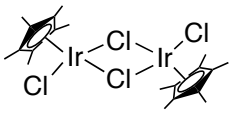
Testing organometallic compounds



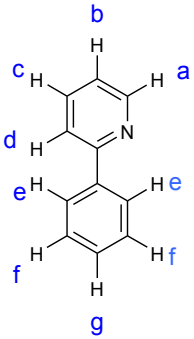
AcONa

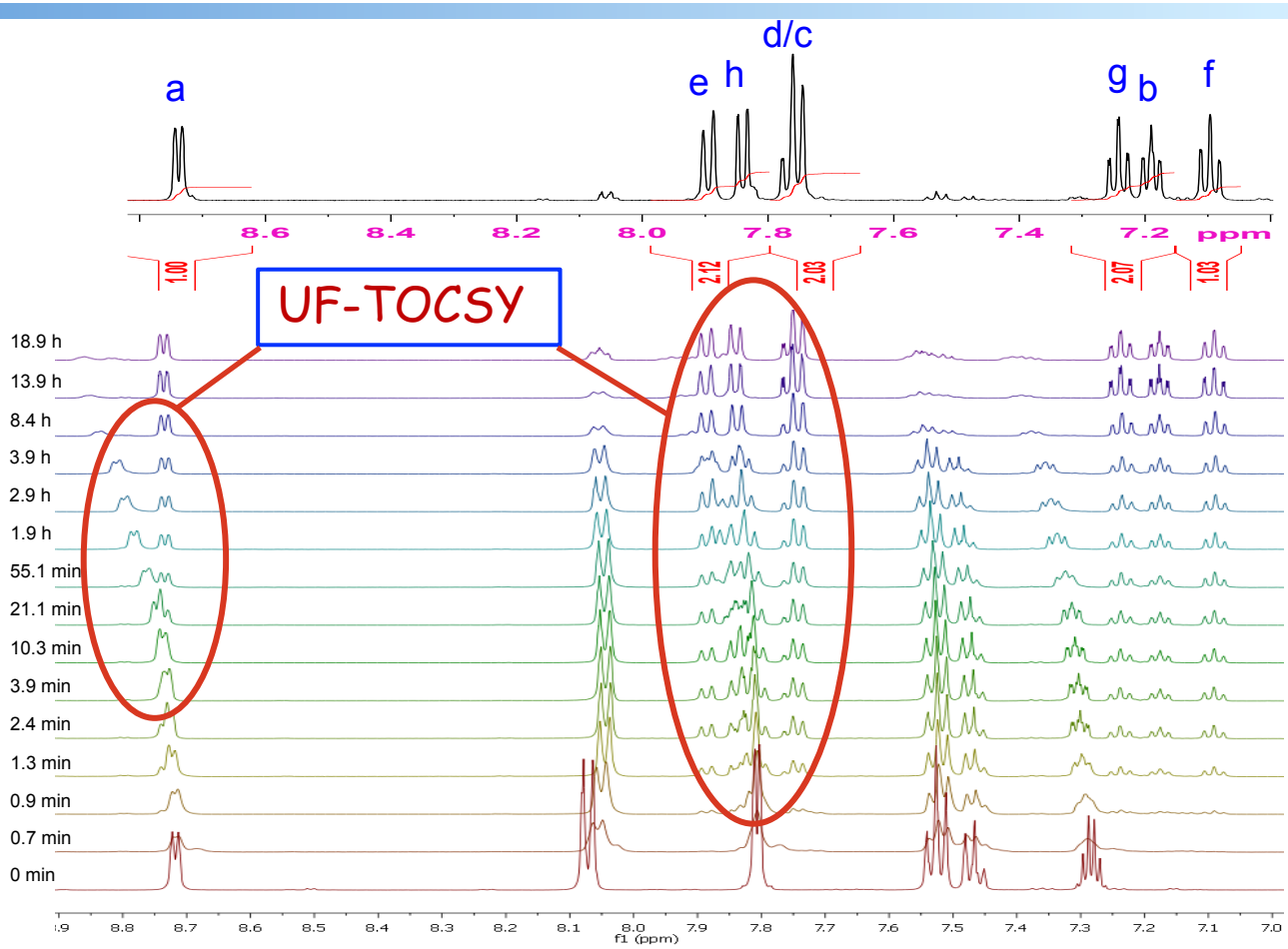
CD_2Cl_2

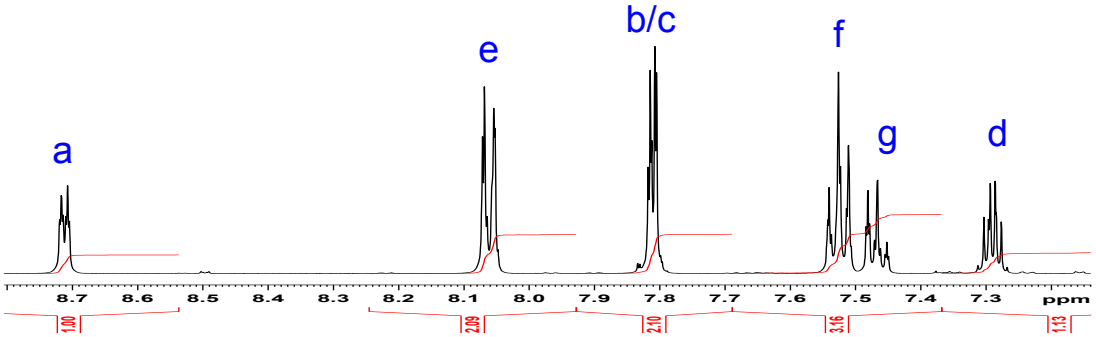
r.t.



+





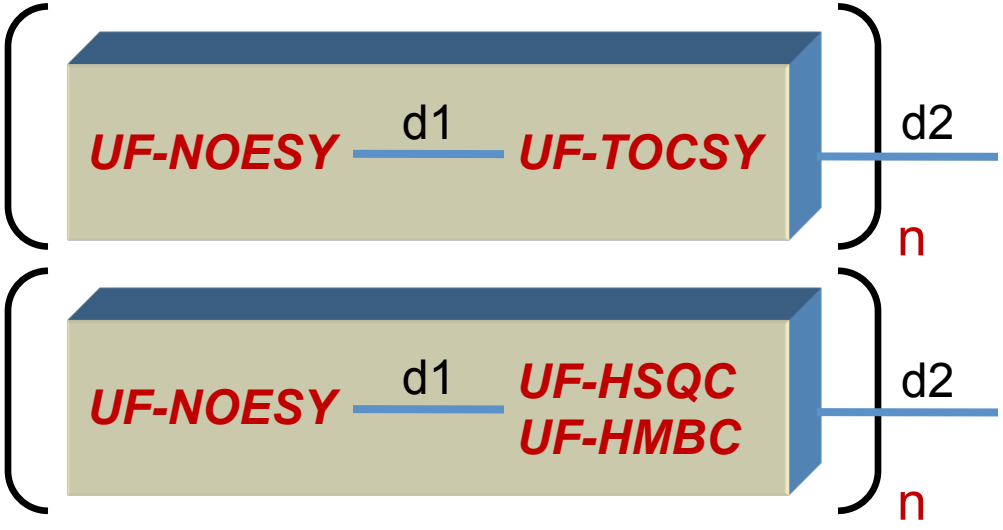


^{1}H-NMR

Strategies for monitoring reactions

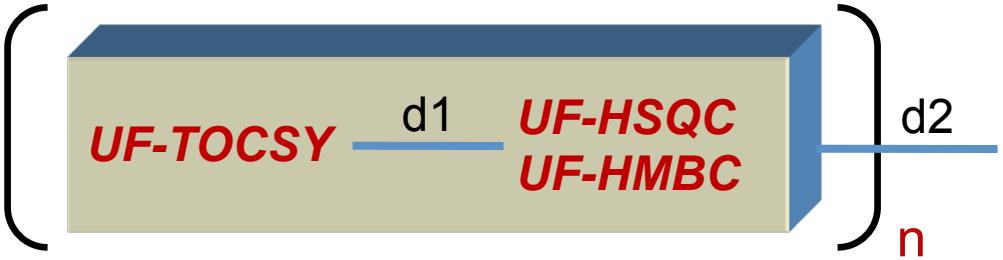
bond formation → *UF-TOCSY, UF-HSQC, UF-HMBC.....*

dipolar interactions → *UF-NOESY ....*

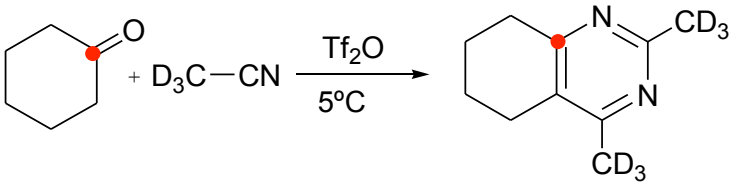


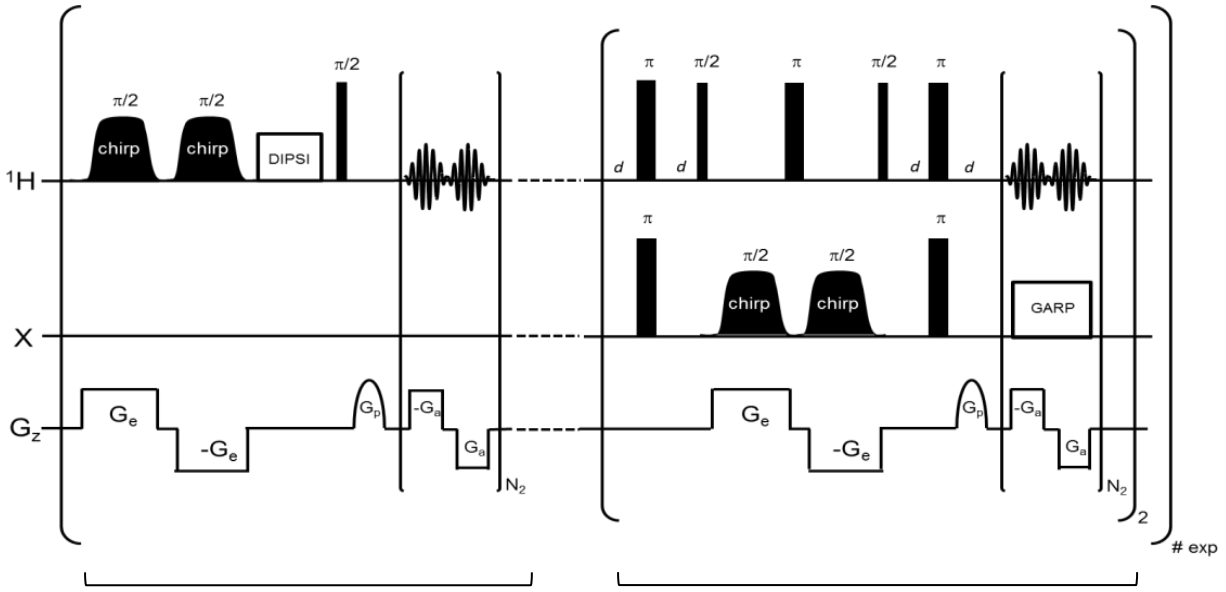
Interactions + Bond formation

A ⟷ B → A — B



Monitoring by alternating dynamic UF-TOCSY-HMBC

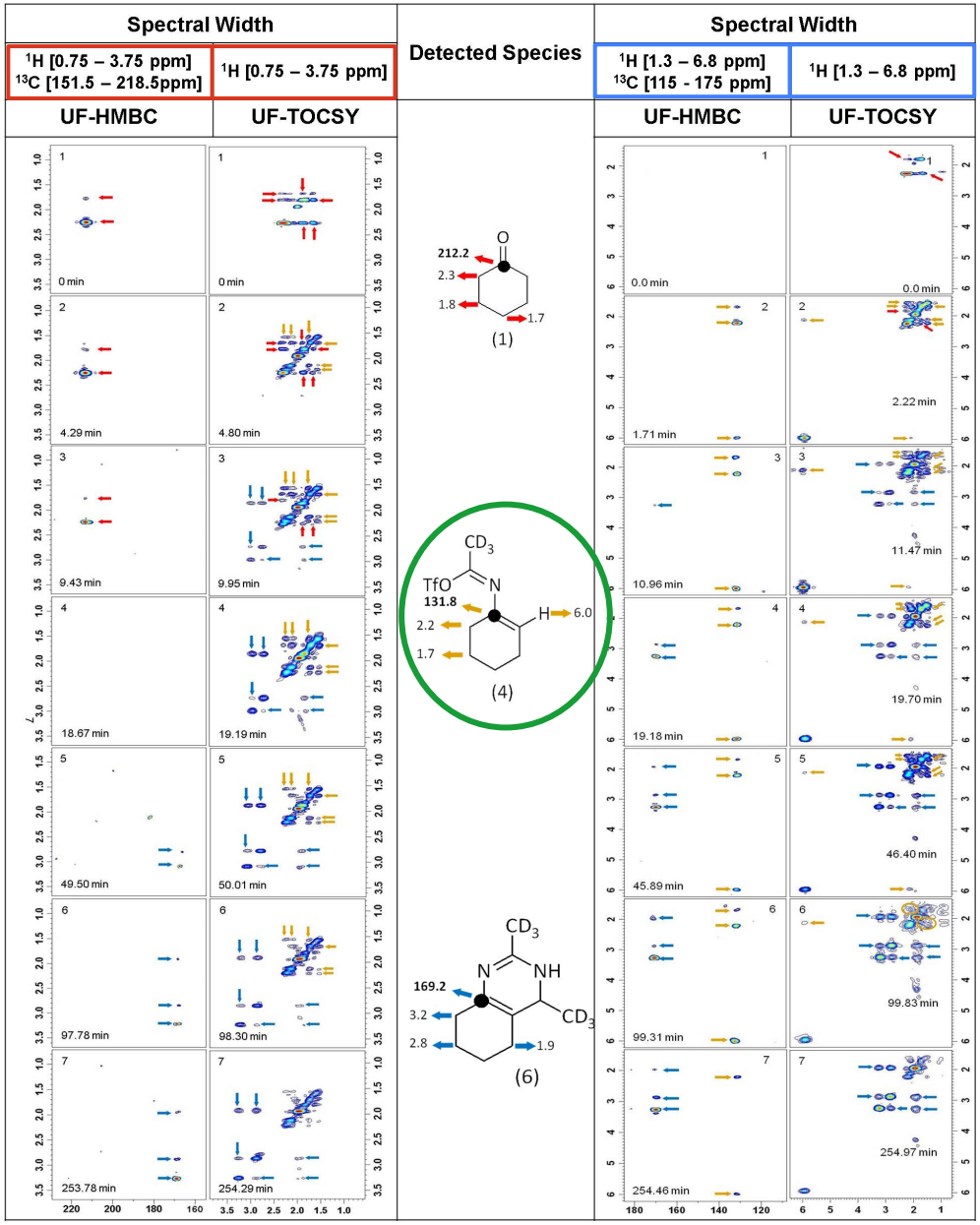




UF-TOCSY

UF-HMBC (2 *scans*)

Monitoring by alternating TOCSY-HMBC



Monitoring organic reactions:

What have permitted UF-NMR spectroscopy?

1. Detection of intermediates in an organic reaction.
2. Information about structure, lifetime, kinetic data, etc.
3. Dipolar interactions can be detected.
4. Standard NMR hardware.

We are studying now systems with:

Low concentrations (<100 mMol)

Short lifetime intermediates (<5s delay)

Unlabeled compounds

New dynamic systems

Combined scalar and/or dipolar monitoring

Monitoring organic reactions:

What can UF-NMR spectroscopy offer?

Are you thinking of applying UF-NMR to your system?

HAVE NO DOUBT: introduce yourself to this adventure.

Simply DO IT!

We can help you.

Acknowledgements

(€) MINECO (Project CTQ2010-61973)

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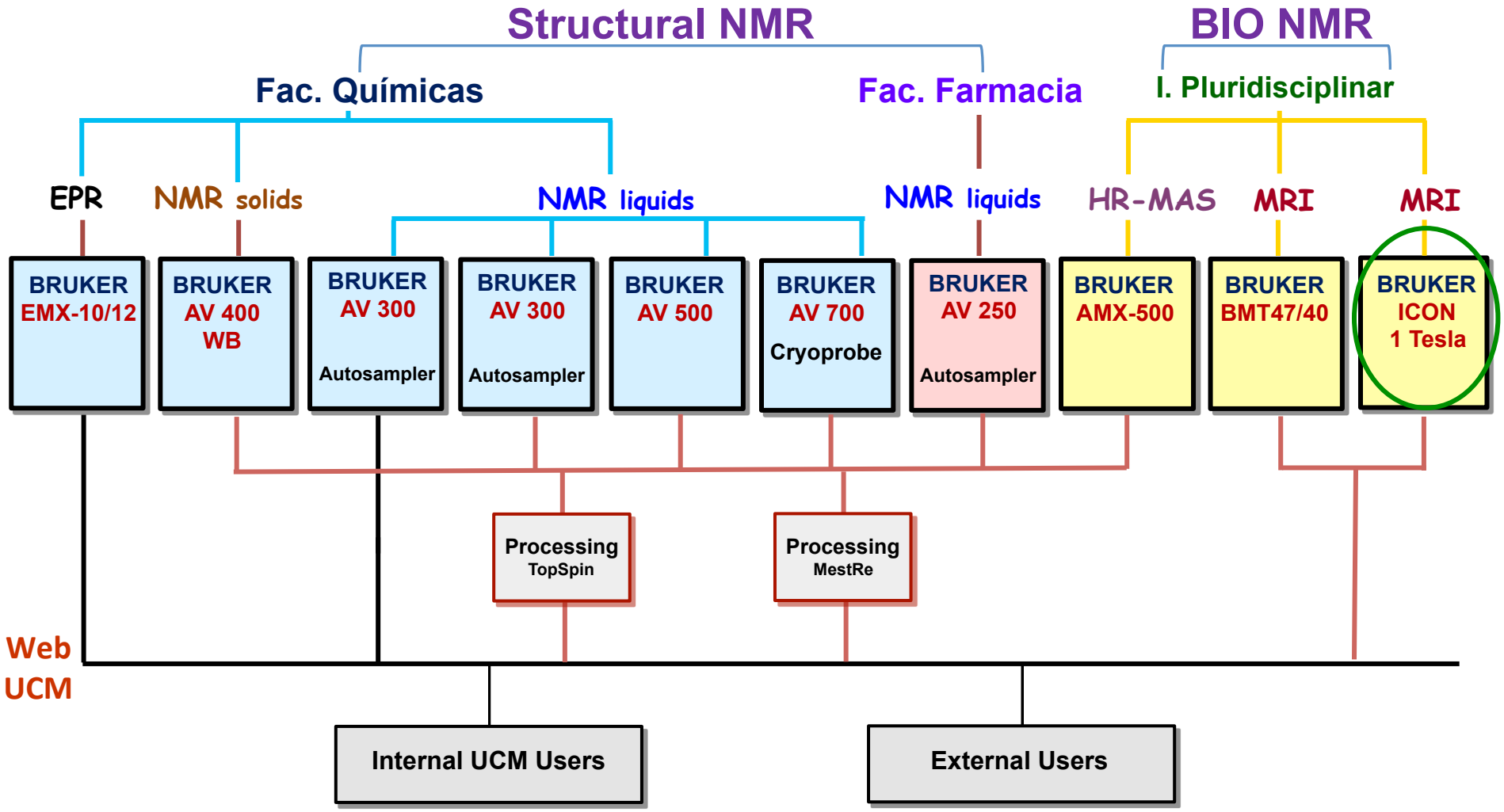
Dra. Elena Sáez Barajas
Ángel Sánchez Vázquez

CAI de RMN y RSE

CAI de RMN y RSE



Small Molecule NMR Conference
September 22nd – 25th, 2013
Santiago de Compostela, Spain

Different attempts to monitor organic reactions in real time

THANK YOU