Unprecedented Structures driven by the Phosphinamide Linkage – A Multinuclear NMR Touch

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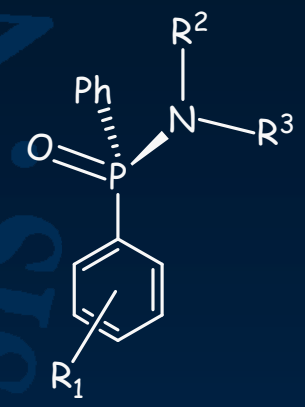
Universidad de Almería (Spain)

EURACT NMR
KARLSRUHE 2010



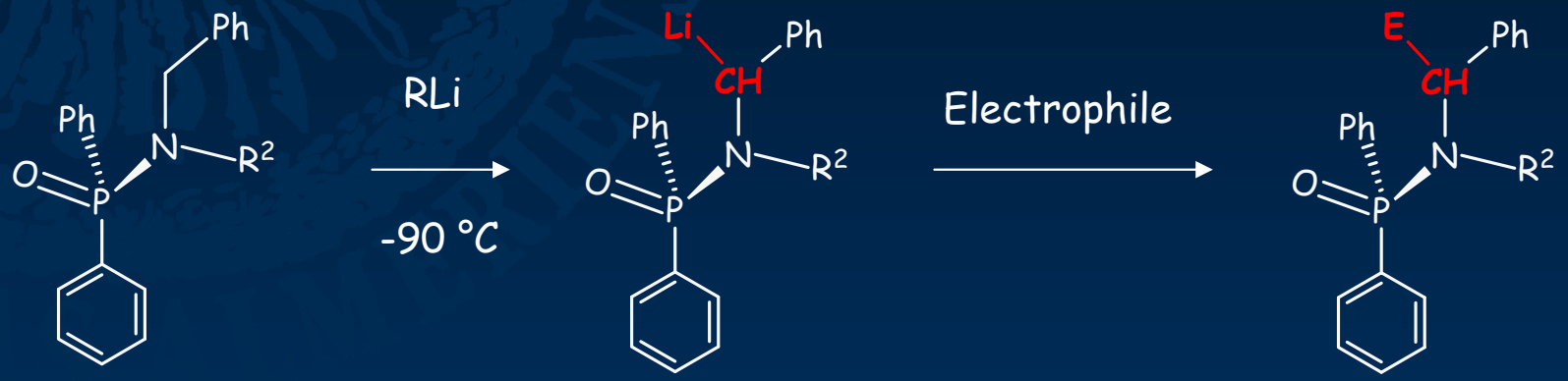
- Analogues having the capability of mimicking the transition state of enzymatic amide formation or hydrolysis.

- They could therefore act as enzymatic inhibitors.

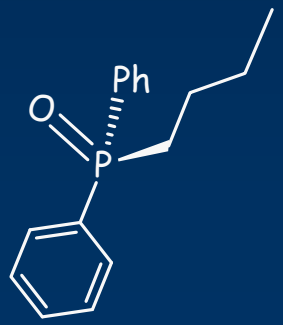
- This potential activity drives us to find some structural diversity.

- And interestingly, phosphinamide reactivity could be selectively tuned depending on the conditions assayed.

1) Diethyl Ether - C_α metalation



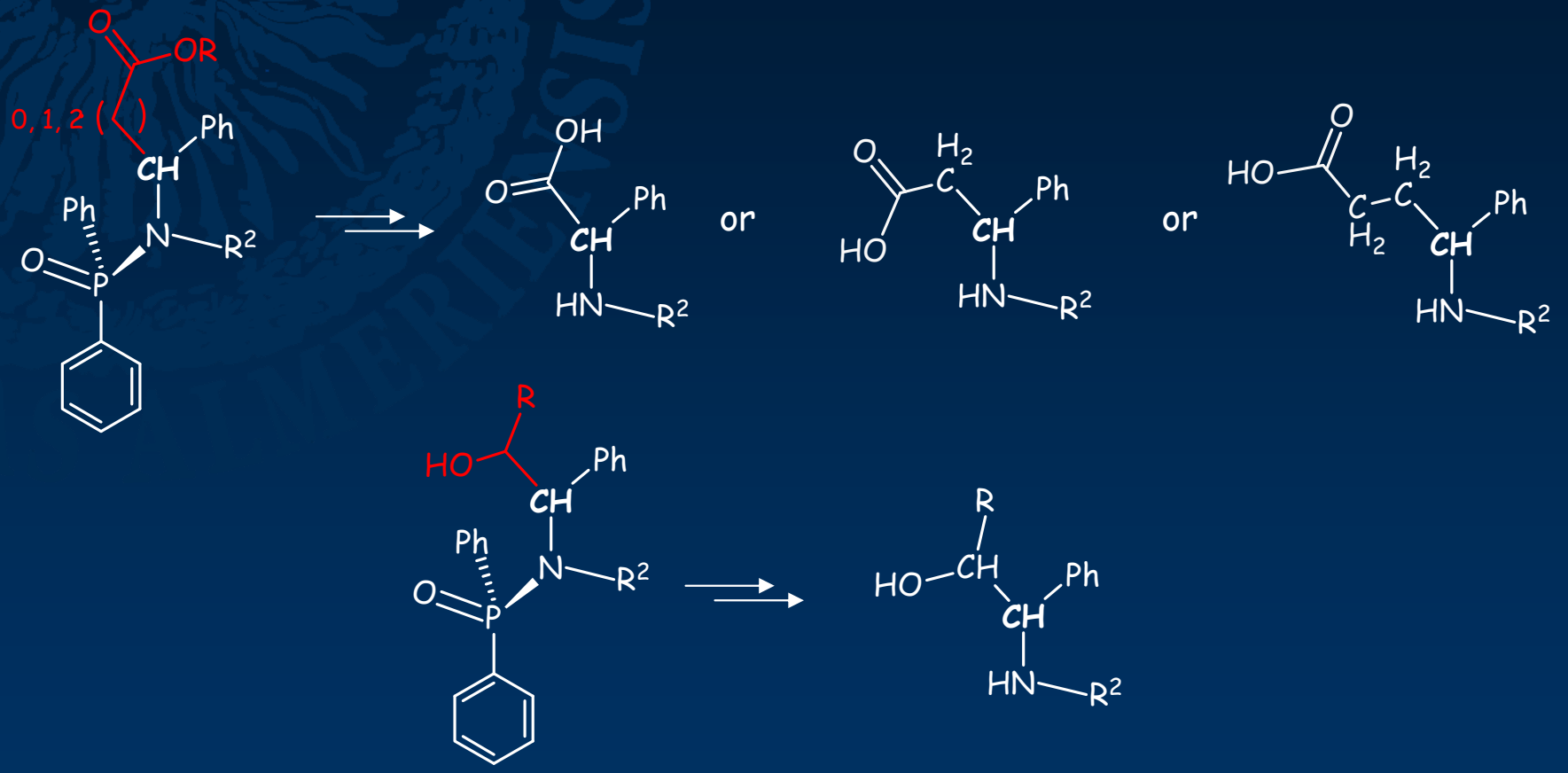
n-BuLi



E = RX, RCHO, $X(CH_2)_nC(O)R$
$RHC{=}CH(O)R$, R_3SnX

Chem. Commun. **2004**, 1142
Org. Lett. **2008**, 10, 537

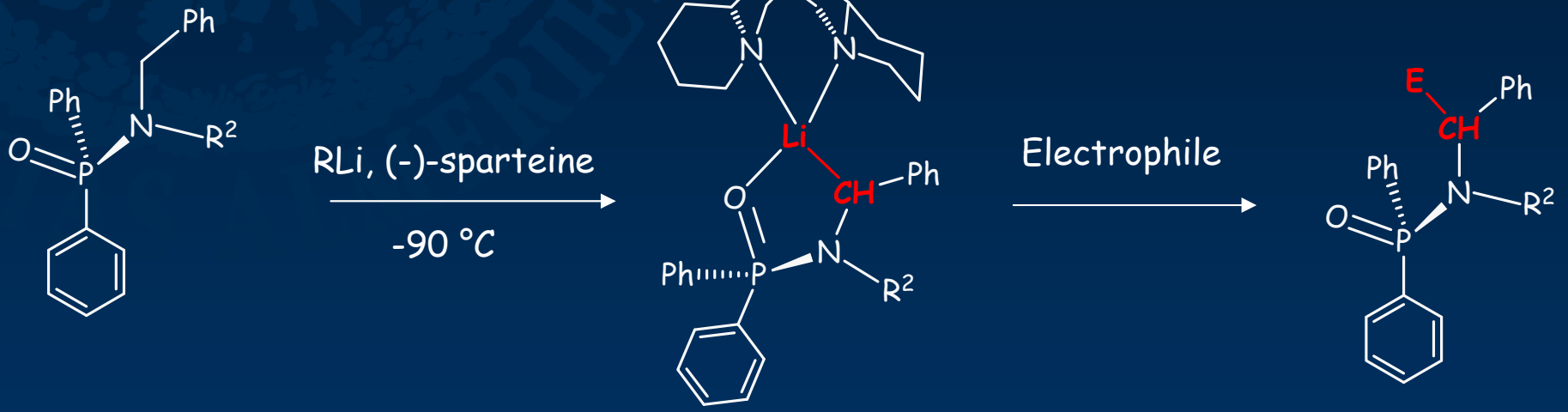
1) Diethyl Ether - C_α metalation



P200601793. (ES) **2006**

Org. Lett. **2008**, 10, 537

1) Diethyl Ether - C_α metalation – Asymmetric Induction

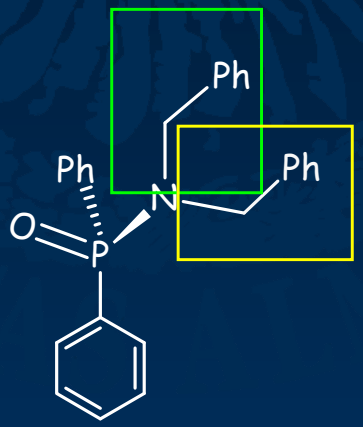


E = RX, RCHO, $X(CH_2)_nC(O)R$
$RHC{=}CH(O)R$, R_3SnX

60 - >99 ee%

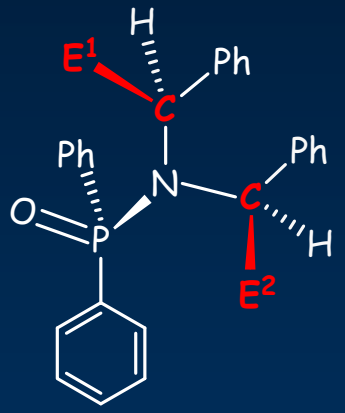
Org. Lett. **2008**, 10, 3195

1) Diethyl Ether - C_α metalation – Double Asymmetric Induction

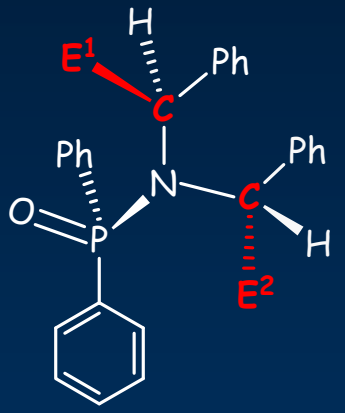


1) RLi, (-)-sparteine, -90 °C
2) Electrophile-1

3) RLi, (-)-sparteine, -90 °C
4) Electrophile-2



+



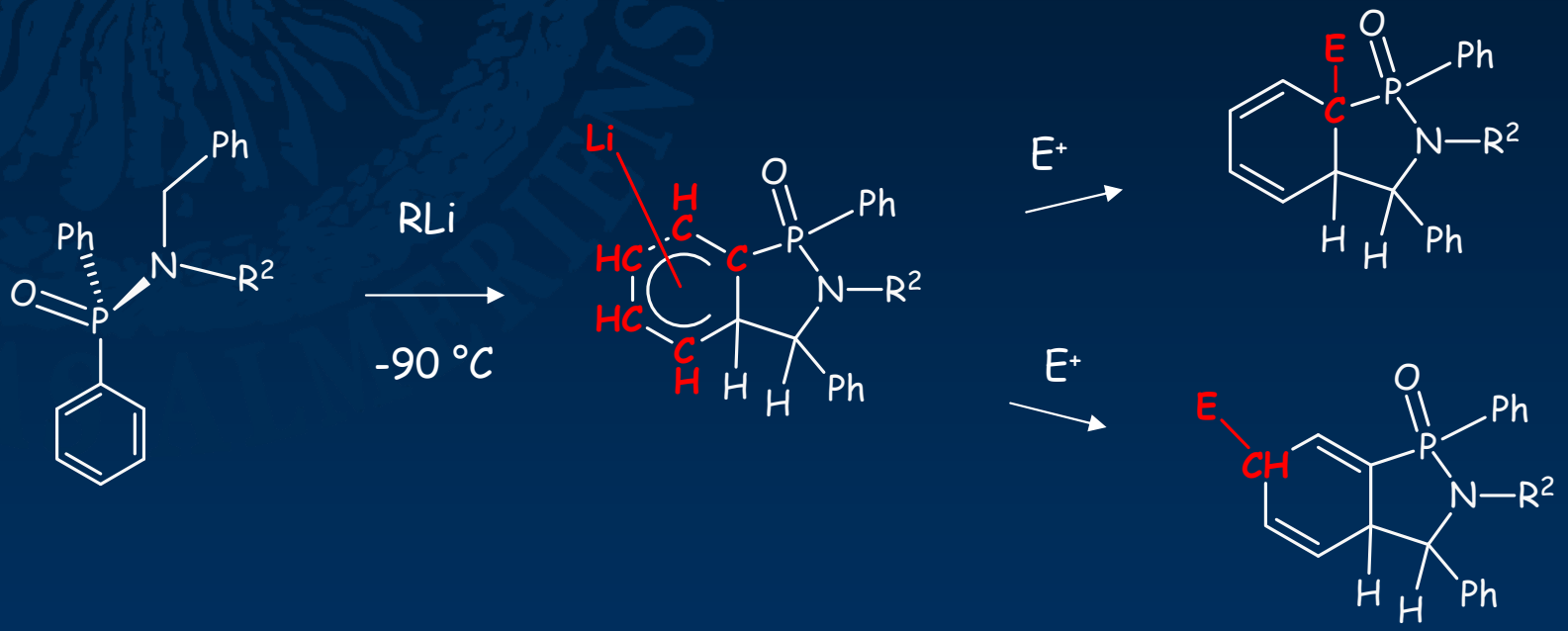
(*S*,*R*) (*R*,*R*)

3-7 : 1

(-)-sparteine

Org. Lett. **2008**, 10, 3195

2) Tetrahydrofuran – Anionic cyclization

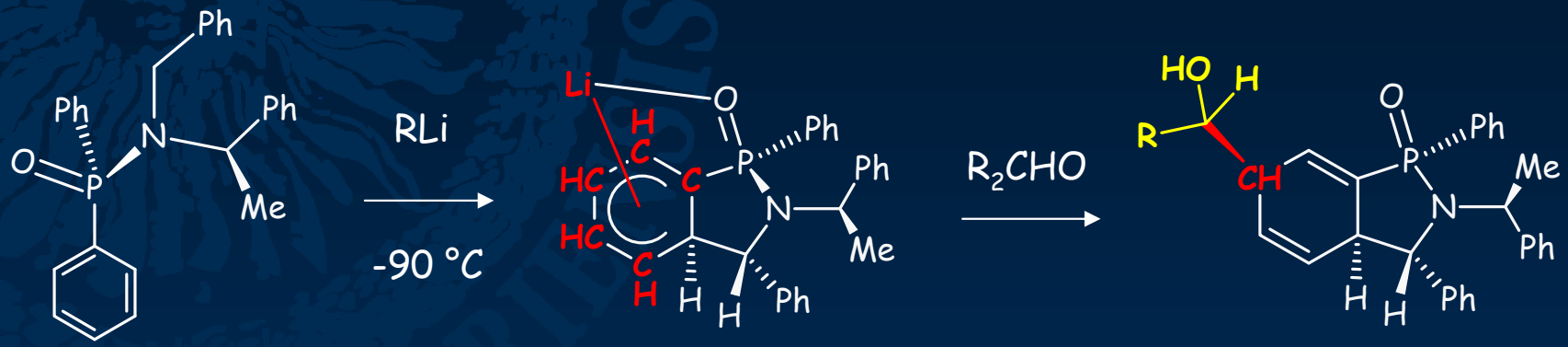


$E^+ = H^+$, RX, RCHO,
RHC=CH(O)R, R_3SnX

Org. Lett. **2001**, *3*, 1339

J. Am. Chem. Soc. **2004**, *126*, 12551

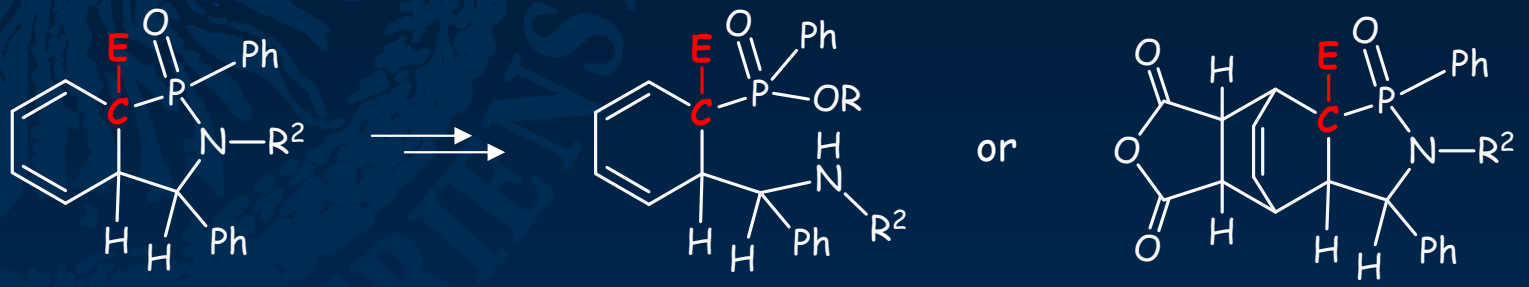
2) Tetrahydrofuran – Anionic asymmetric cyclization

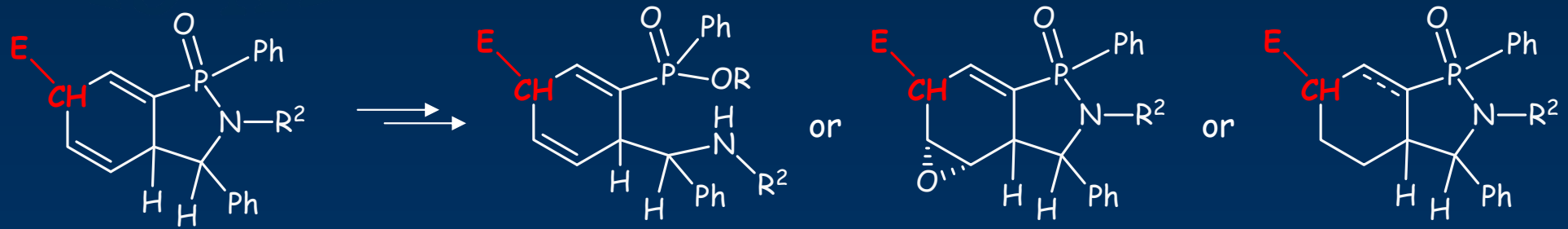


R^2CHO	(*S*)	(*R*)	Rdto. (%)	*ee* (%)
PhCHO	88 %	12 %	98	>99
FuCHO	81 %	19 %	91	>99
$(CH_3)_2CHCHO$	78 %	22 %	78	>99

Chem. Commun. **2005**, 5408

2) Tetrahydrofuran – Anionic cyclization

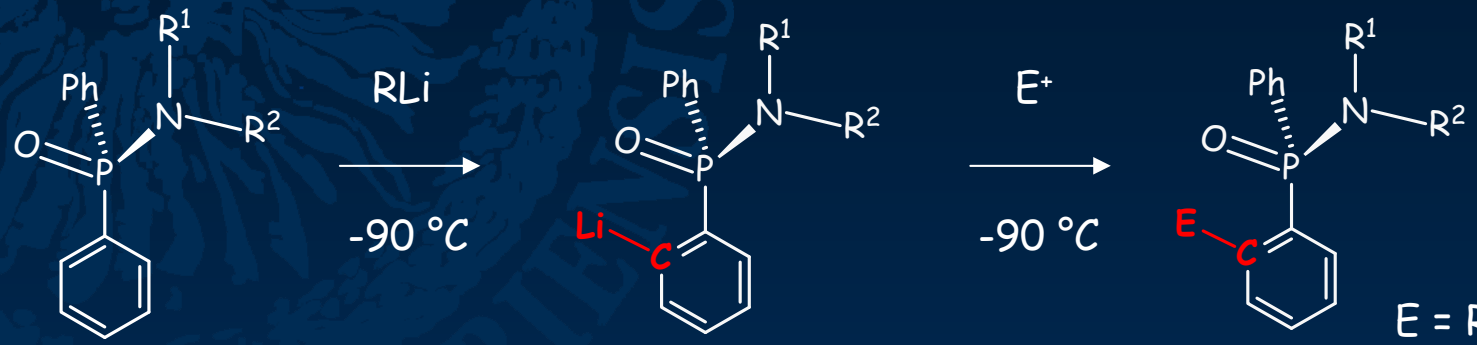


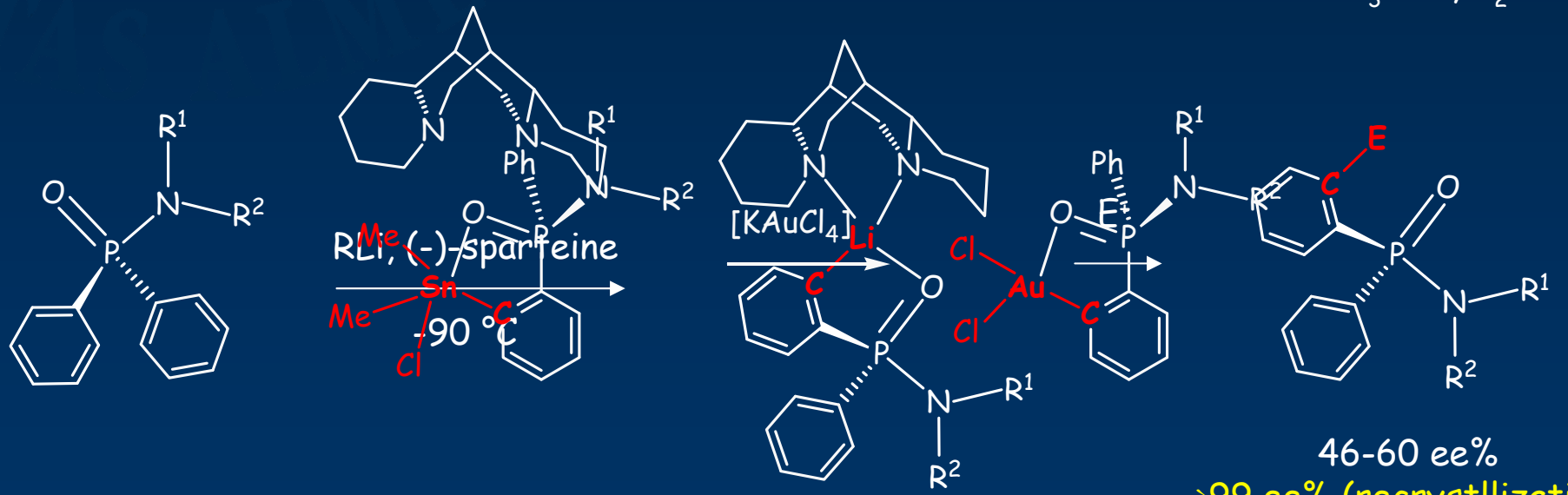


J. Org. Chem. **2003**, *68*, 4472

PCT/WO2008/0003809A1, **2008**

3) Tetrahydrofuran – *Ortho* metalation

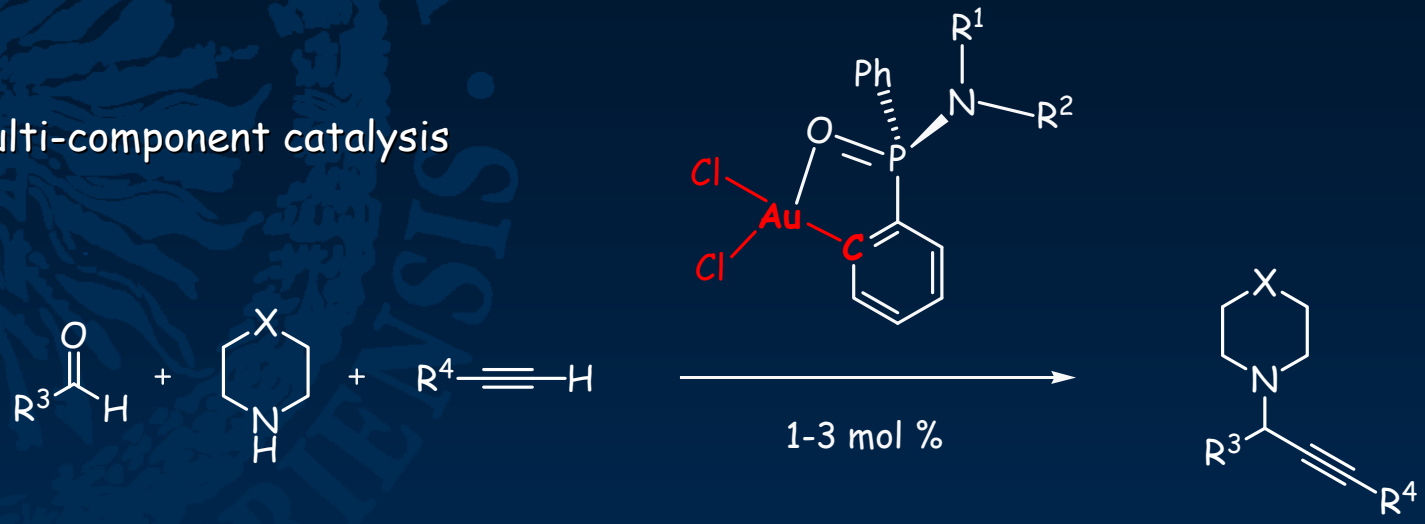


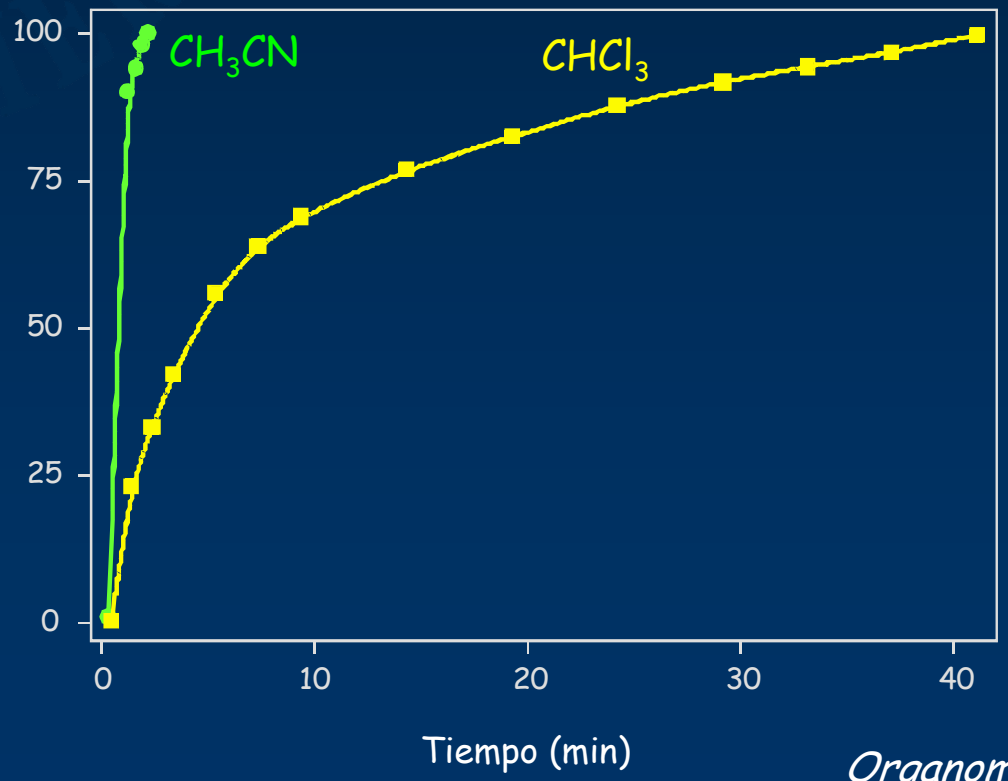


Org. Lett. **2010**, *12*, ASAP

3) Tetrahydrofuran - *Ortho* metalation

A^3 multi-component catalysis

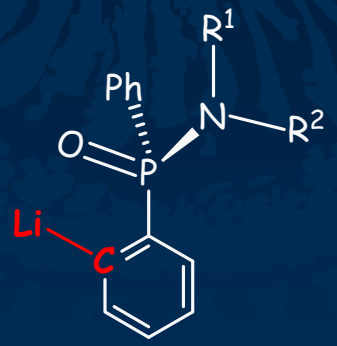




Organometallics **2009**, *28*, 1739

PGSE Diffusion NMR

1



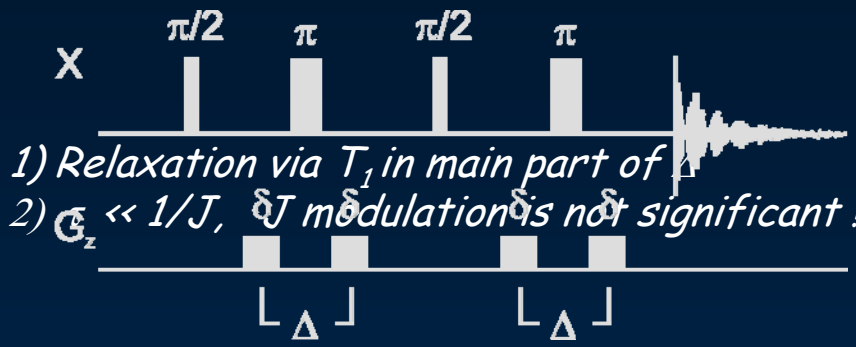
SOLUTION STRUCTURE ??

Multinuclear NMR

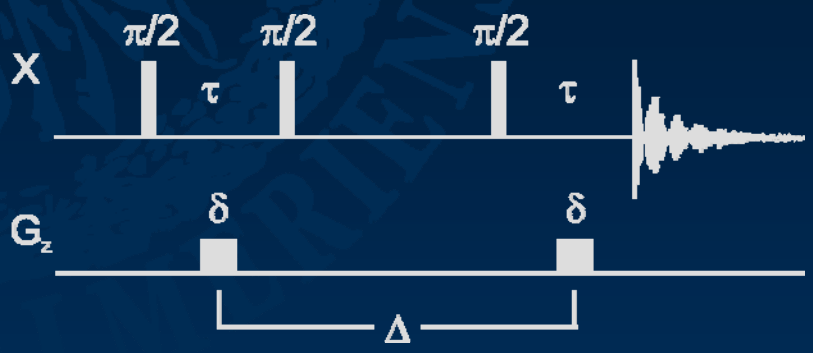
X/Y Shift Correlation

PGSE as a tool

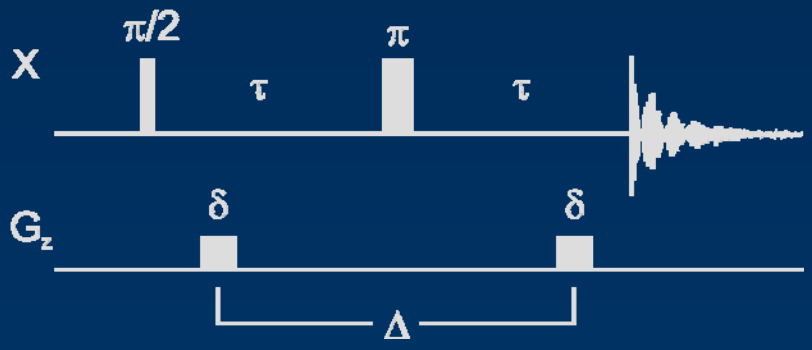
Stimulated Echo (STE), 1995



1) Relaxation via T_1 in main part of Δ
2) τ << 1/J, J modulation is not significant !!



J-compensated, 2010



AX $\varphi_J = 4\pi\ J_{AX}\ 2\ \tau$

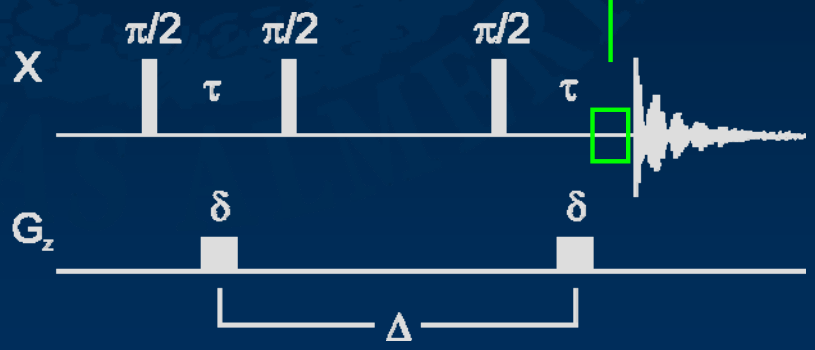
$2\tau = n\ (1/2J_{AX})$

$2\tau < 1/2J_{AX}$ Phase Distorsion

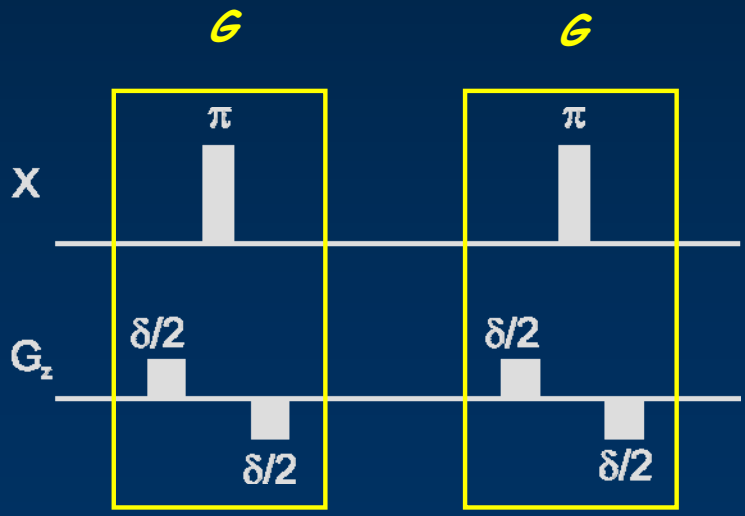
Stejskal-Tanner, 1965

PGSE as a tool

Stimulated Echo (STE), **1995**



Longitudinal Eddy current Delay, **1998**



Bipolar Pair Pulses, **1993**

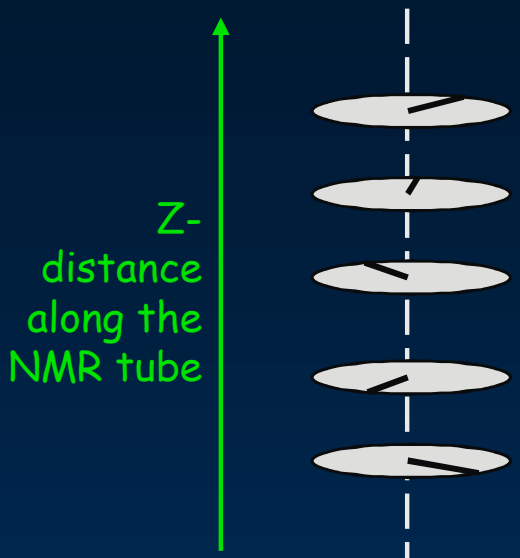
PGSE as a tool

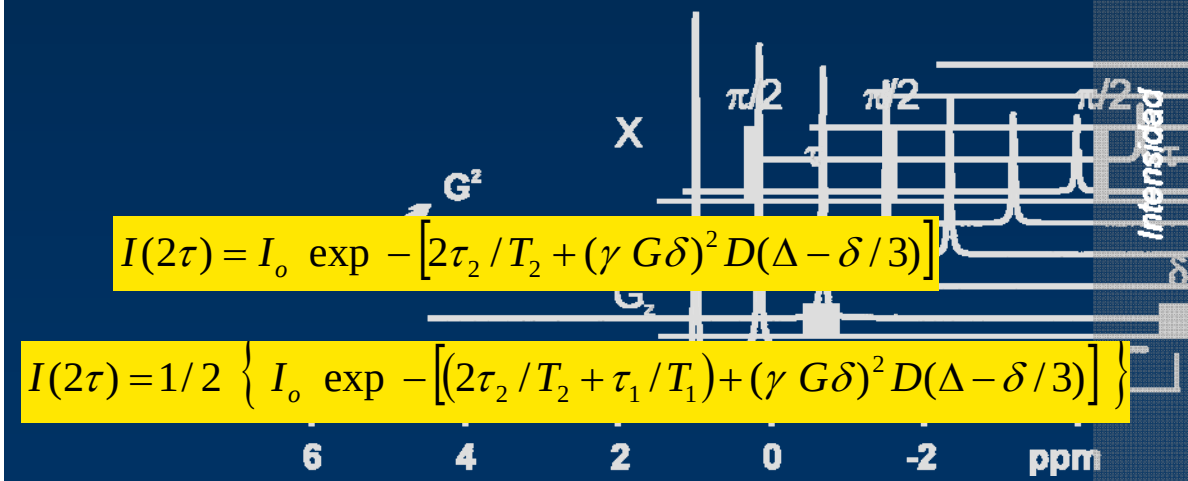
The effect of the gradient over w_L

$$\omega_L = \gamma B_o + \gamma G z$$

The dephase angle experienced depends on the position along the z axis, that is given by

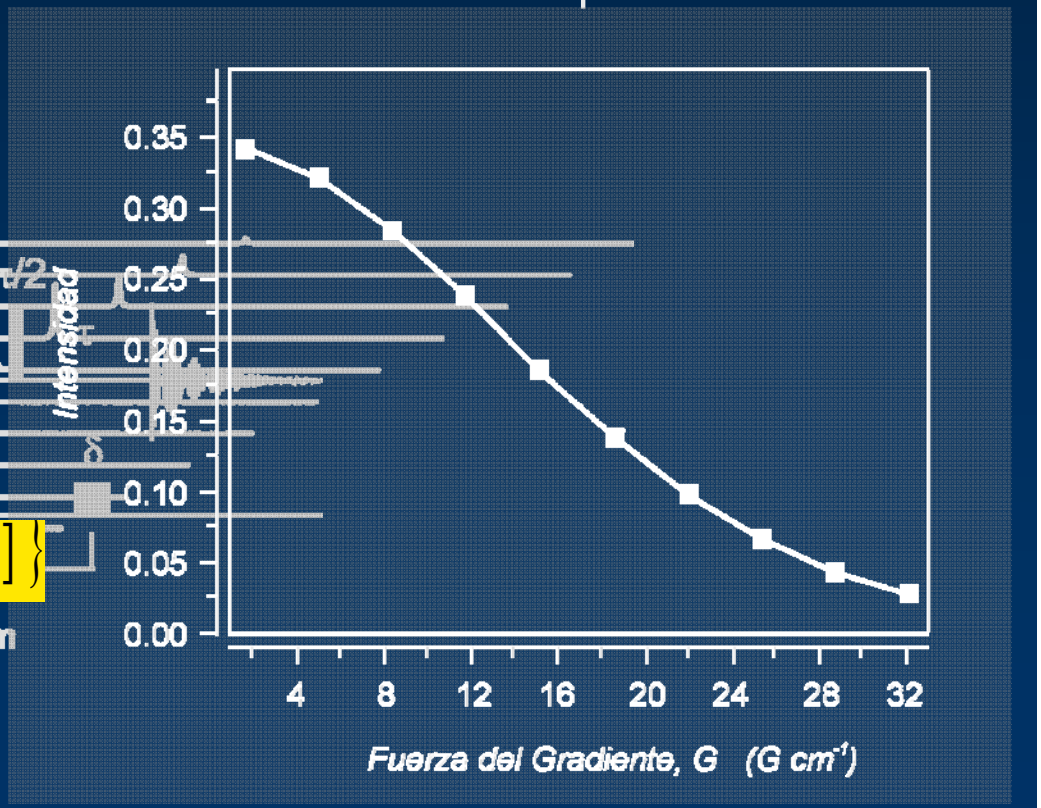
$$\varphi_z = \delta \gamma G z$$





$$I(2\tau) = I_o \exp -\left[2\tau_2 / T_2 + (\gamma G\delta)^2 D(\Delta - \delta/3)\right]$$

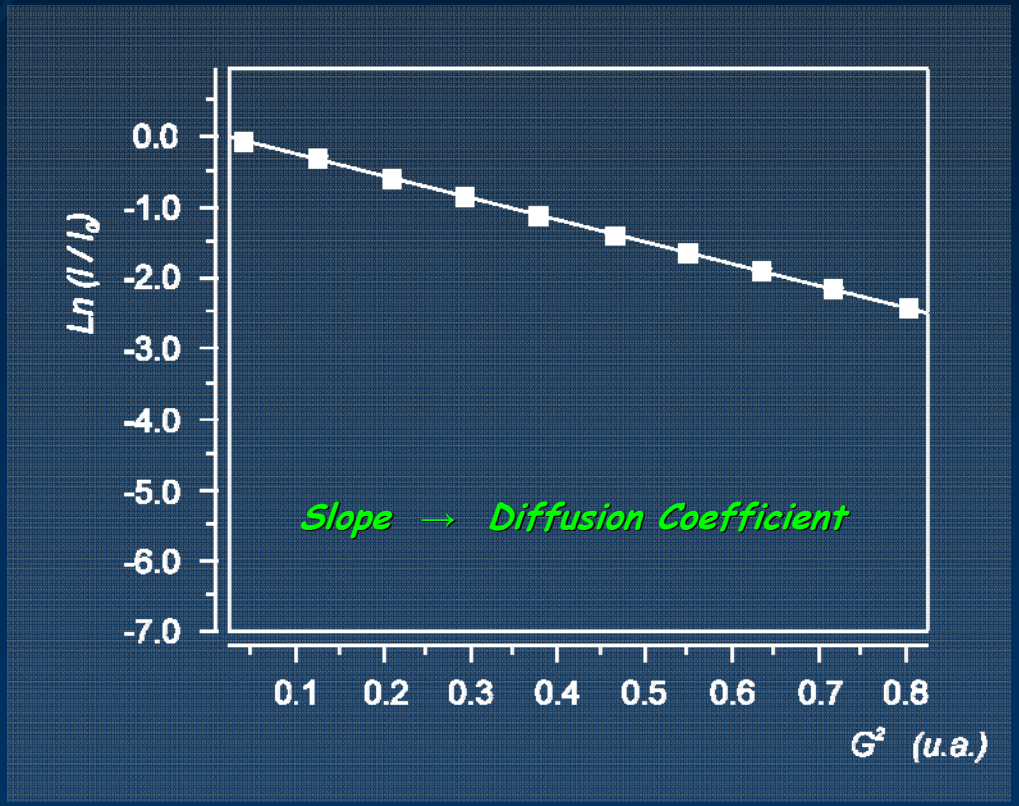
$$I(2\tau) = 1/2 \left\{ I_o \exp -\left[(2\tau_2 / T_2 + \tau_1 / T_1) + (\gamma G\delta)^2 D(\Delta - \delta/3)\right] \right\}$$



PGSE as a tool

Diffusion Coef.

$$\ln(I / I_o) = -(\gamma\delta)^2 G^2 D(\Delta - \delta/3)$$



Hydrodynamic Radius from the Diffusion Coefficient

The diffusion coefficient is defined by $D = k_B T / f$

For a sphere of known r radius, the friction factor is

Stokes Equation $f = 6\pi\eta\, r$

Stokes-Einstein Equation $D = \dfrac{k_B T}{6\pi\eta\, r}$

For molecules with radii below 5 Å, semi-empirical expressions can be used that take into account the effects of the solvent of choice

$$c = 6\times\left(\frac{3r_d}{r_H} + \frac{1}{\left(1+{r_d}/{r_H}\right)}\right)^{-1}$$

$$c = 6\times\left[1+\left(0.695\times\left(\frac{r_d}{r_H}\right)^{2.234}\right)\right]^{-1}$$

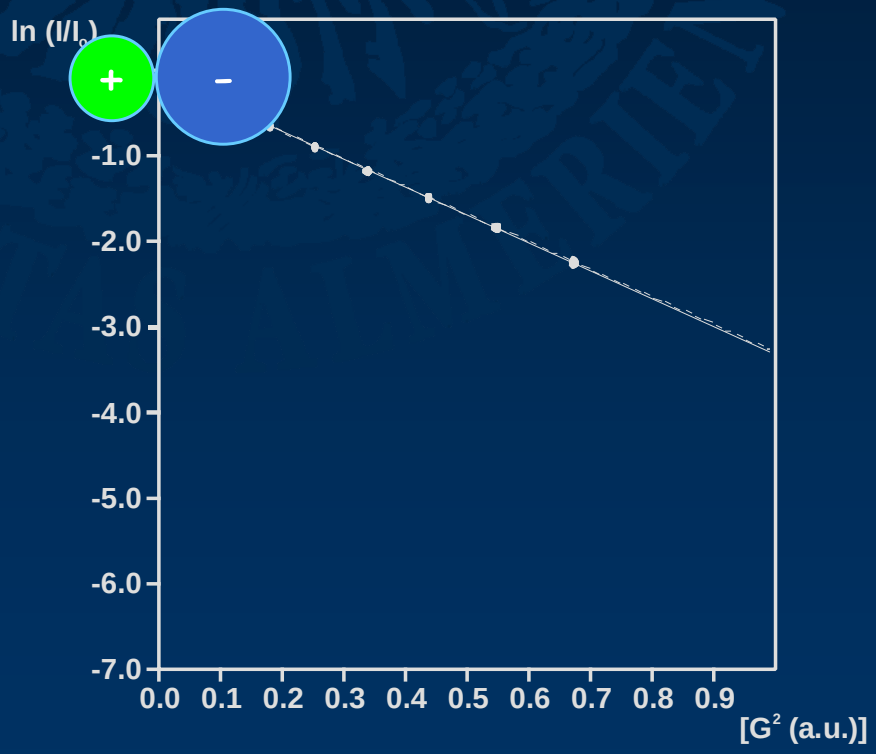
J. Phys. Chem. **1984**, *88*, 5118.
Phys. Chem. **1987**, *91*, 3612.

Diffusion ----- Molecular sizes !!

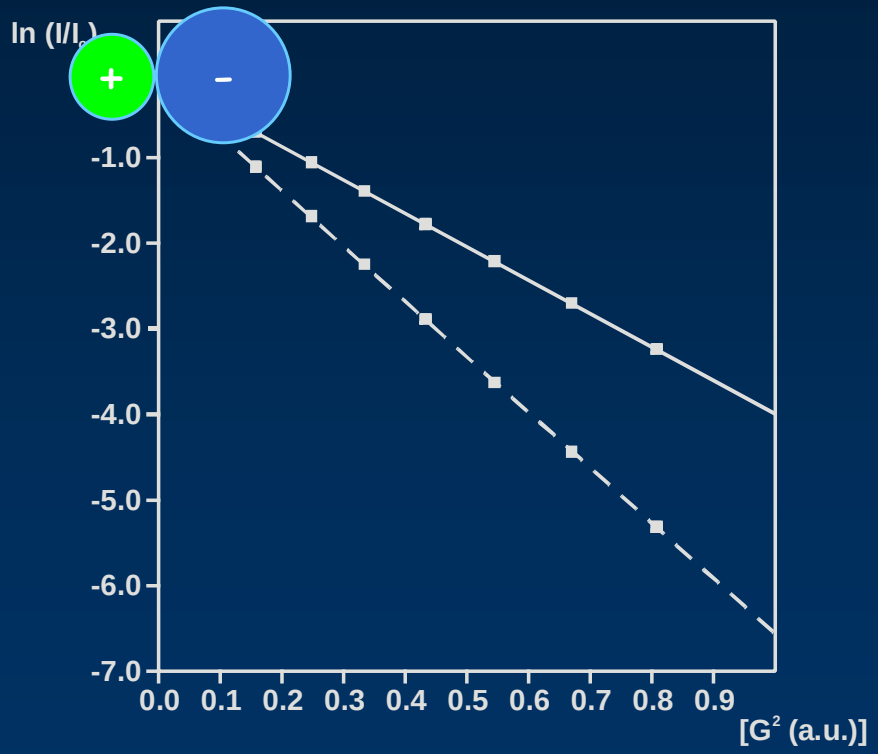
Ion Pairing

Aggregation

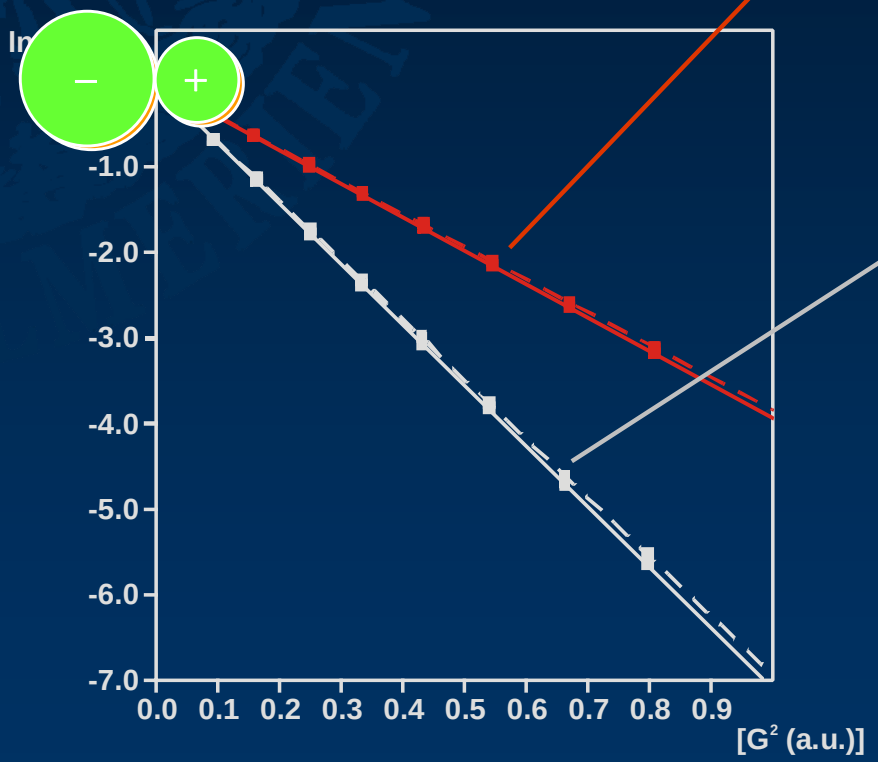
Contact Ion Pair



Solvent Separated Ion Pair



Aggregation



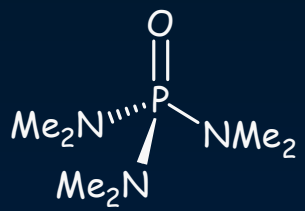
Cation ($^{6/7}$Li)
Anion (^{1}H, ^{19}F, ^{31}P)

Cation ($^{6/7}$Li)
Anion (^{1}H, ^{19}F, ^{31}P)

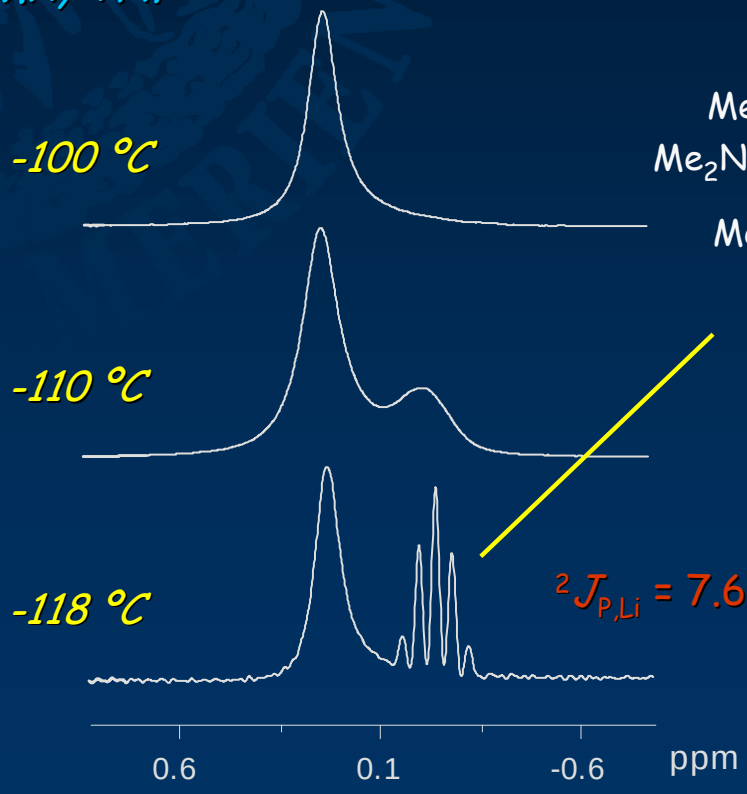
Aggregate 1

Aggregate 2

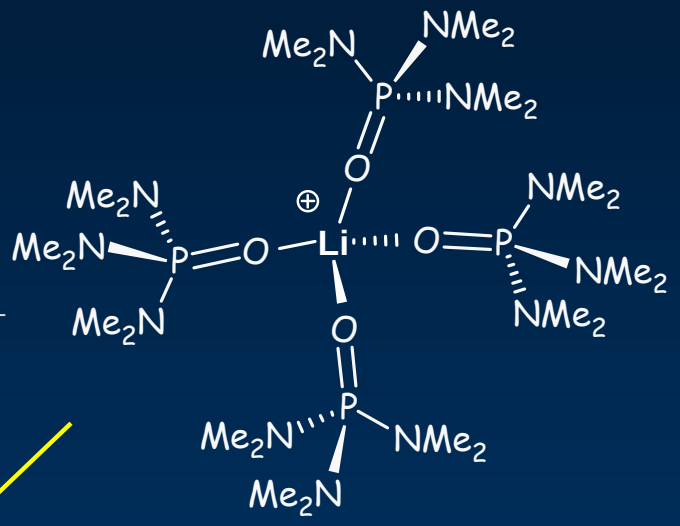
LiCl System /



^{7}Li NMR, THF



$^{2}J_{P,Li}$ = 7.6 Hz



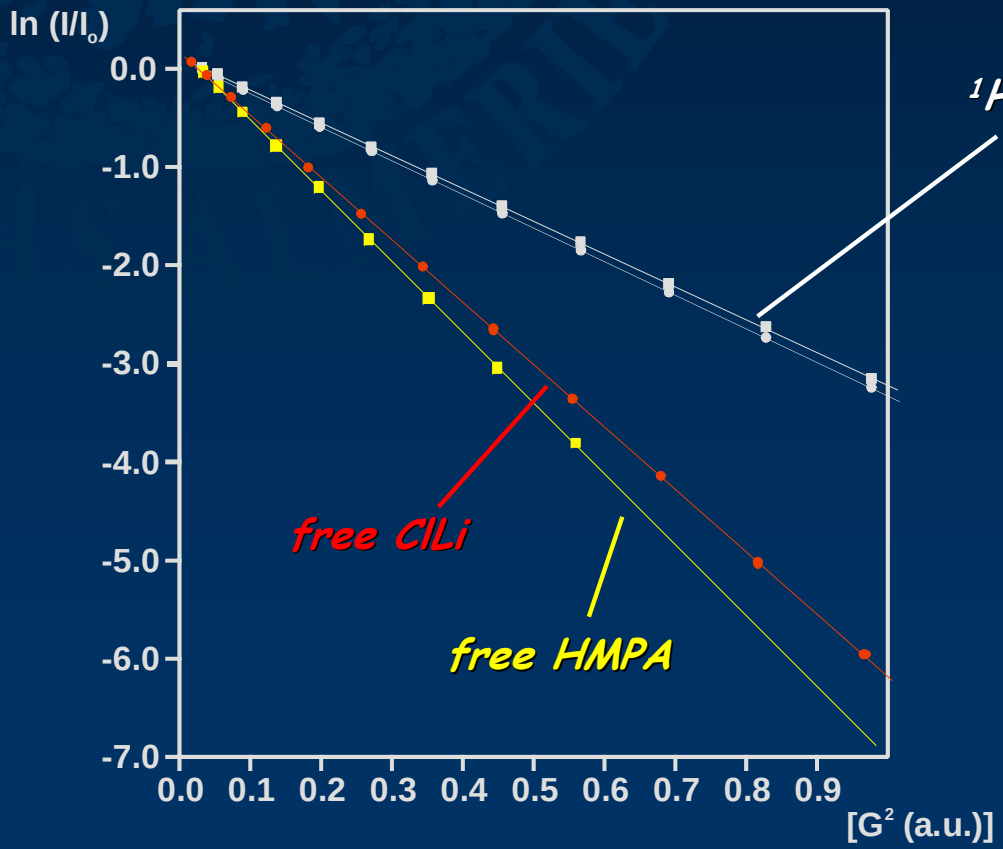
Chem. Eur. J. **2005**, *11*, 1495-1506

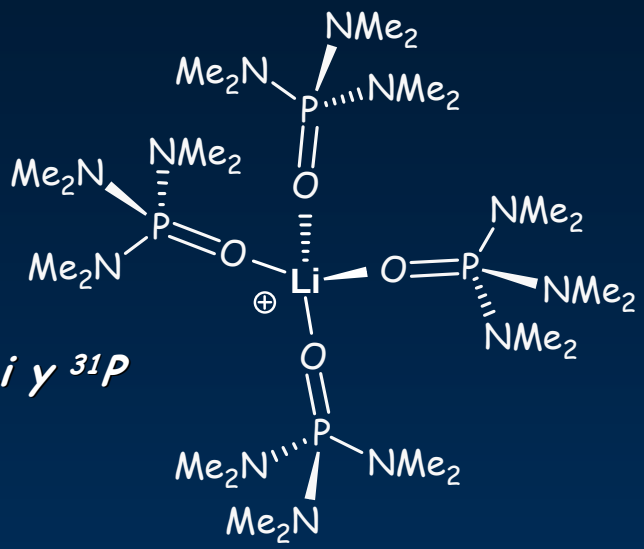
PGSE NMR, THF, 60 mM, -118 °C (concentric tubes)

$D\ (Li\{HMPA\}_4) = 0.142 \times 10^{-10}\ m^2\ s^{-1}$

$D\ (free\ LiCl) = 0.252 \times 10^{-10}\ m^2\ s^{-1}$

$D\ (free\ HMPA) = 0.351 \times 10^{-10}\ m^2\ s^{-1}$





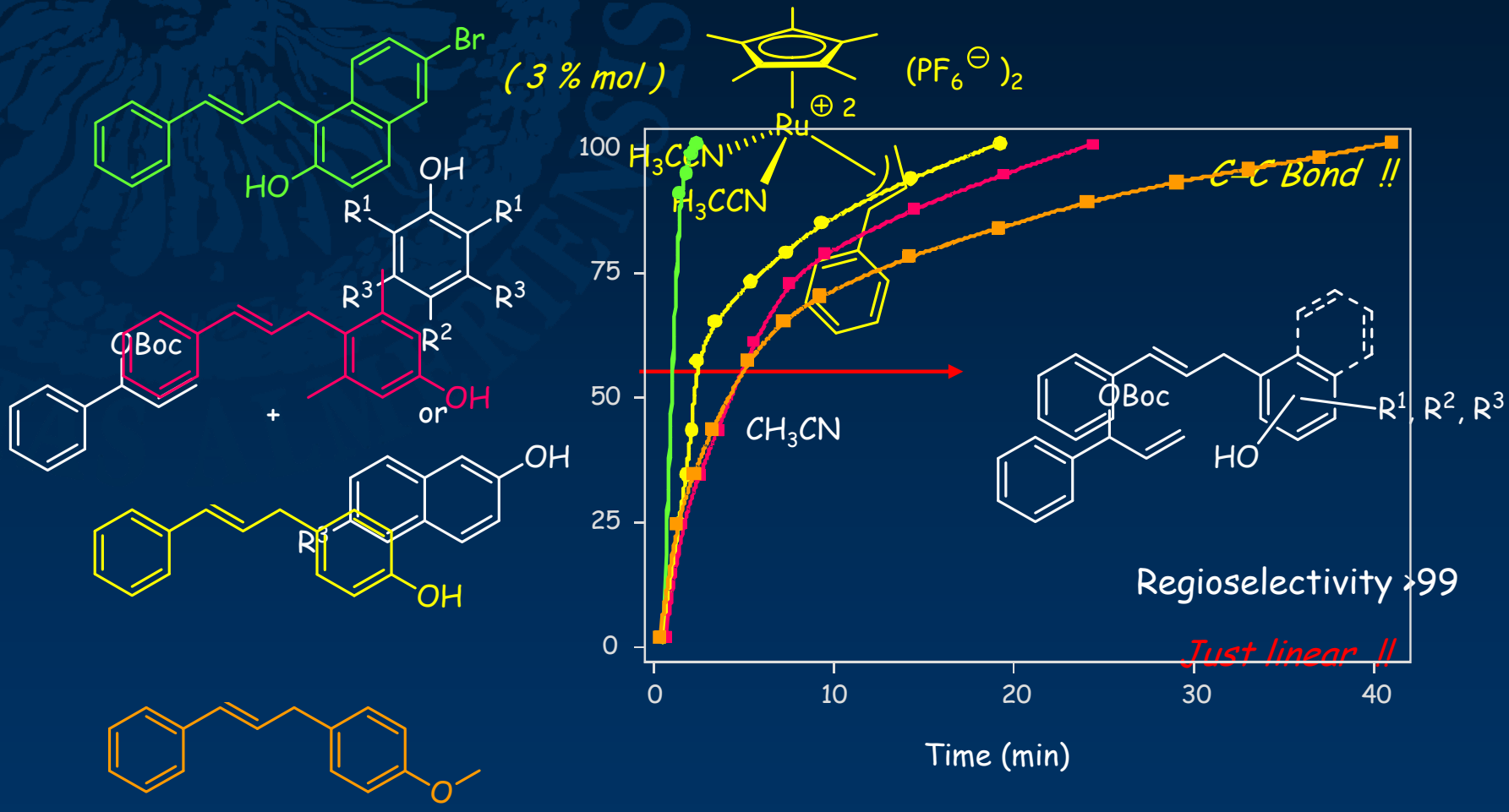
$r_H(Li\{HMPA\}_4) = 7.0$ Å

$r_H(free\ LiCl = 4.3$ Å

$r_H(free\ HMPA) = 3.1$ Å

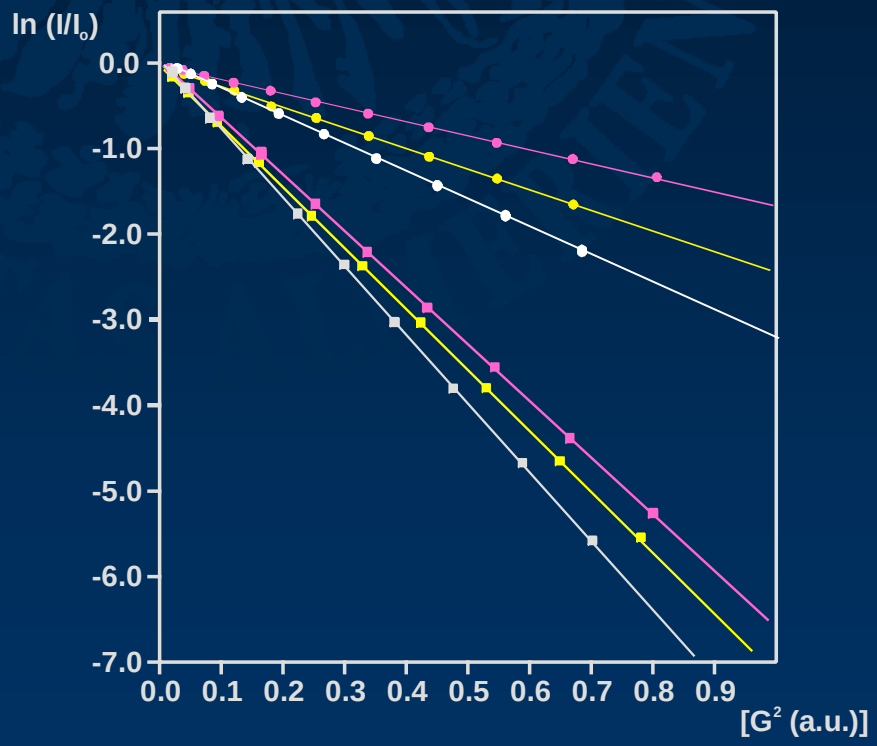
Chem. Eur. J. **2005**, *11*, 1495-1506

Ruthenium-catalyzed Fridel-Crafts allylation reaction



Angew. Chem., Int. Ed. **2006**, *45*, 6386

PGSE NMR, CH_3CN, 2-20 mM, RT



D (Cation) (2 mM) = 12.07 × 10^{-10} m^2 s^{-1}
D (Anion) (2 mM) = 23.50 × 10^{-10} m^2 s^{-1}

r_H (Cation) = 5.4 Å
r_H (Anion) = 2.8 Å

D (Cation) (10 mM) = 11.82 × 10^{-10} m^2 s^{-1}
D (Anion) (10 mM) = 22.69 × 10^{-10} m^2 s^{-1}

r_H (Cation) = 5.5 Å
r_H (Anion) = 3.1 Å

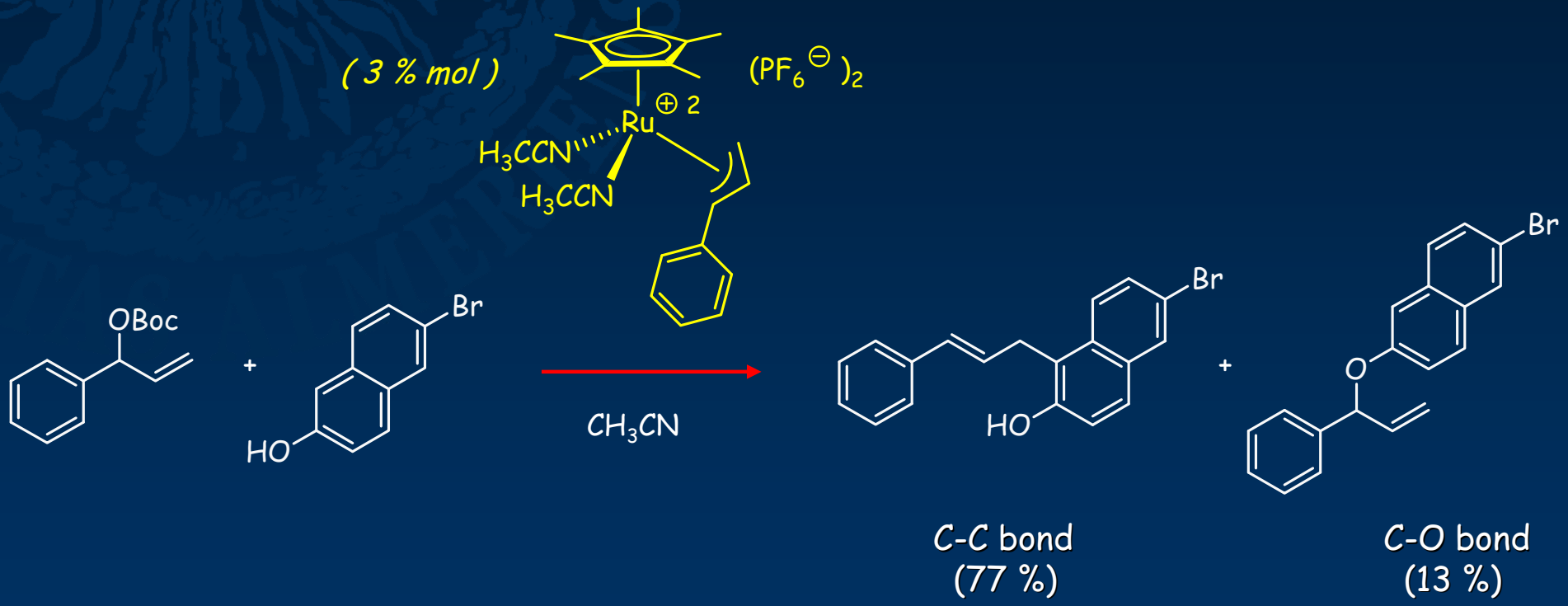
D (Cation) (20 mM) = 11.49 × 10^{-10} m^2 s^{-1}
D (Anion) (20 mM) = 21.57 × 10^{-10} m^2 s^{-1}

r_H (Cation) = 5.7 Å
r_H (Anion) = 3.5 Å

Organometallics **2006**, *25*, 4520

Same catalysis but at different concentration !!

From 10 mM to 0.4 mM !

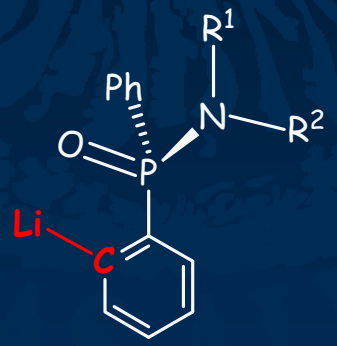


C-C bond
(77 %)

C-O bond
(13 %)

Angew. Chem., Int. Ed. **2006**, *45, 6386*

PGSE Diffusion NMR



SOLUTION STRUCTURE ??

2

Multinuclear NMR

X/Y Shift Correlation

Multinuclear NMR: X/Y Shift Correlation Methods

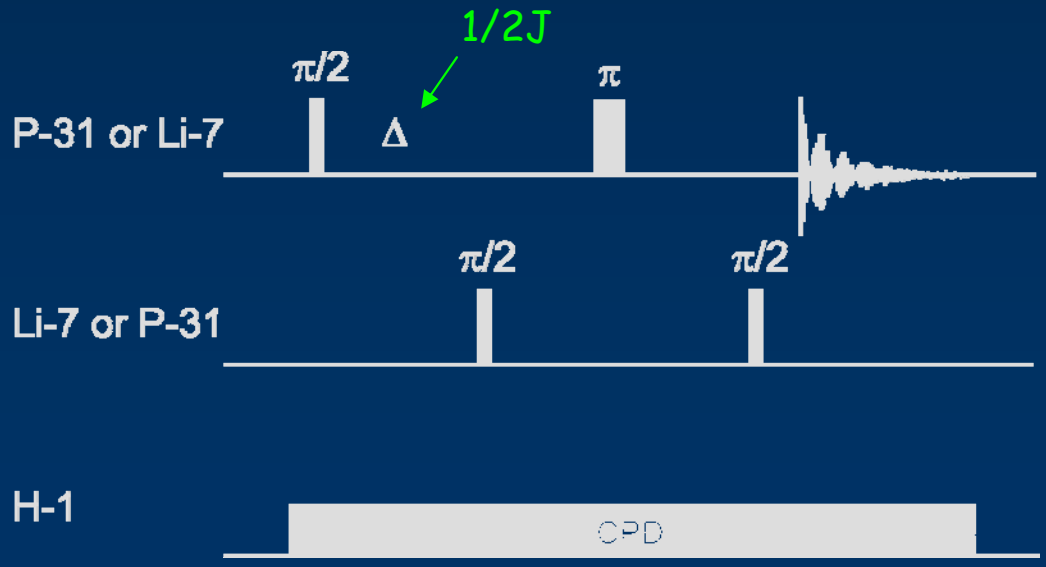
The sensitivity of any heteronuclear NMR experiment is related to γ of starting and detected nuclei, among others parameters

$$S/N \propto \gamma_{start}\gamma_{detect}^{3/2}[1-\exp\{1/T_{1,start}\times D1\}]\times NS$$

Indirect measurements = $\gamma^{5/2}$

Polarization transfer = γ_{start} x $(\gamma_{detect})^{3/2}$

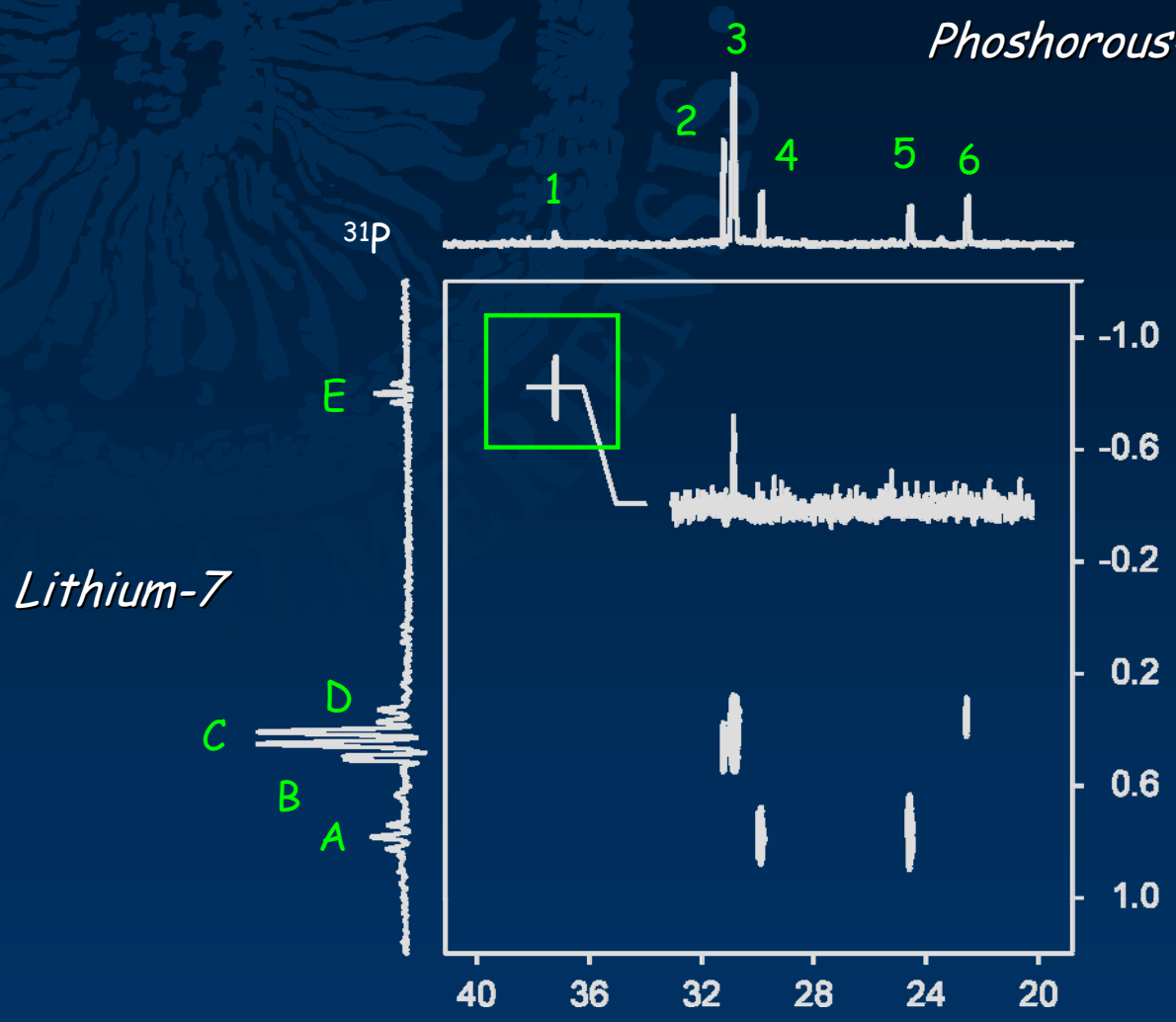
In lithiated phosphinamides systems, we wanted to setup the ^{7}Li(^{31}P)/^{31}P(^{7}Li) Shift correlation experiment.

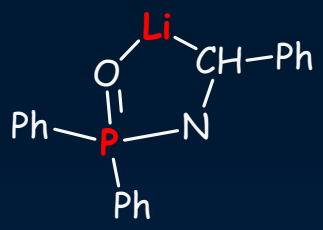


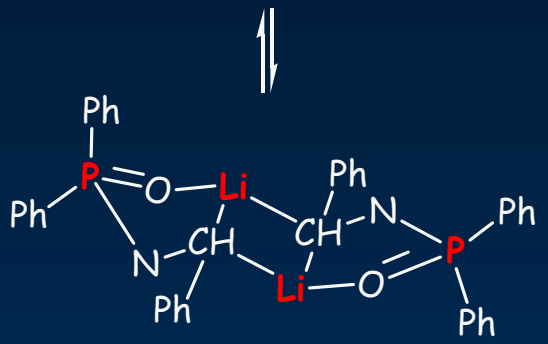
(R_c(P-31)/R_c(Li-7) ~ 2.5

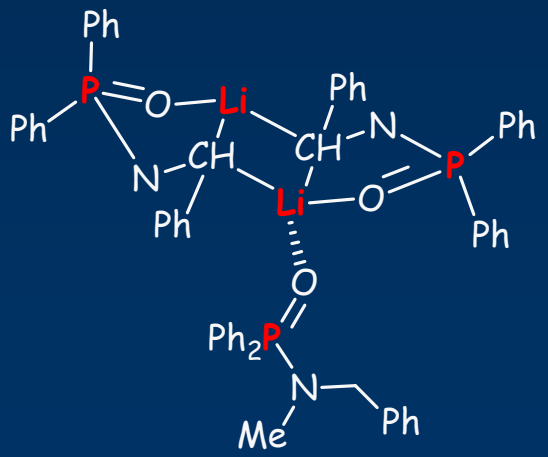
Li-7 (I=3/2) / P-31 (I=1/2)

^{31}P-detected ^{7}Li HMQC NMR, -100 °C, 0.1 M, Et_2O-d_{10}





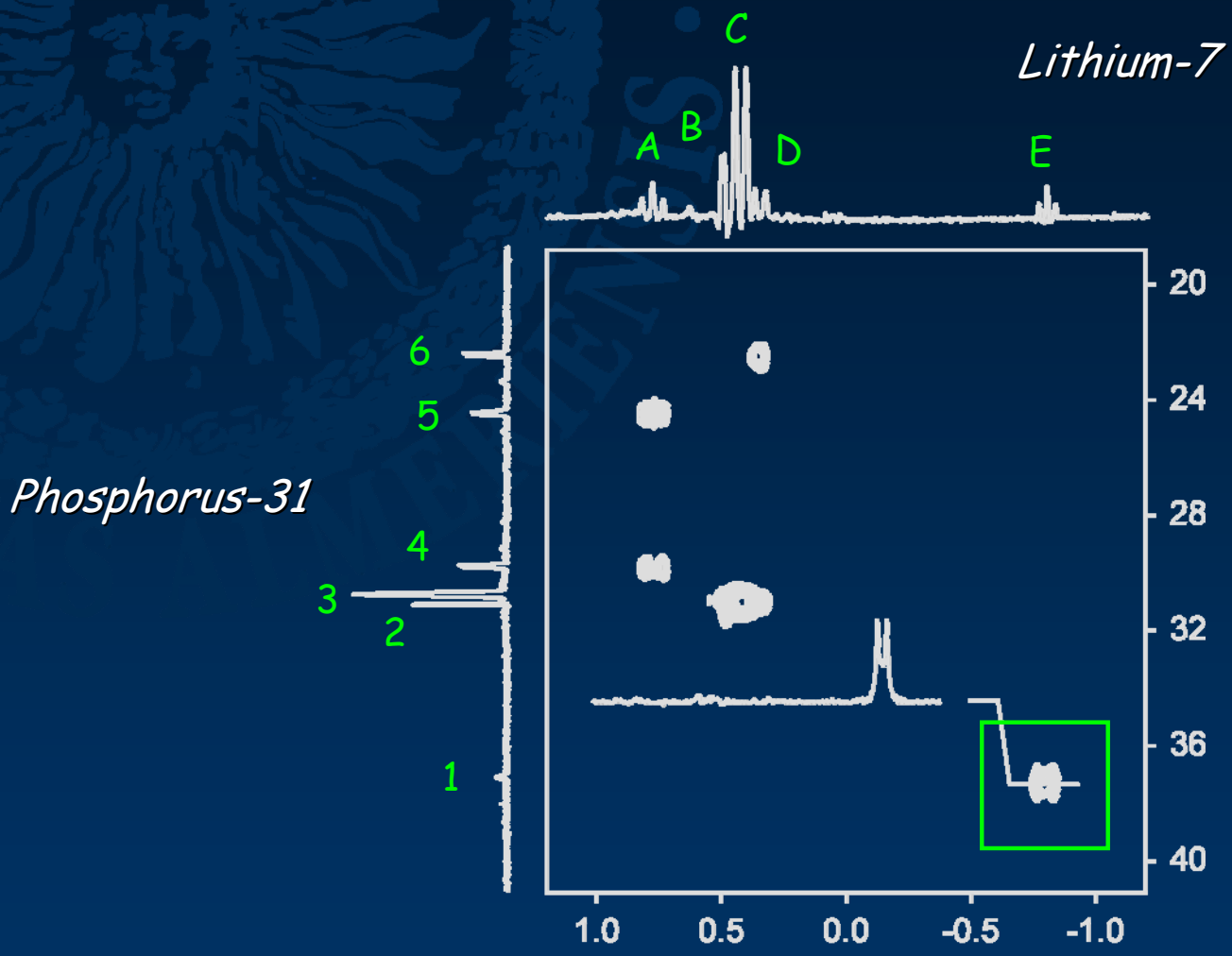




Experimental time = 2 h
S/N (cross-peak 1-E) = 20

Chem. Commun. **2007**, 1142

^{31}P-detected ^{7}Li HMQC NMR, -100 °C, 0.1 M, Et_2O-d_{10}

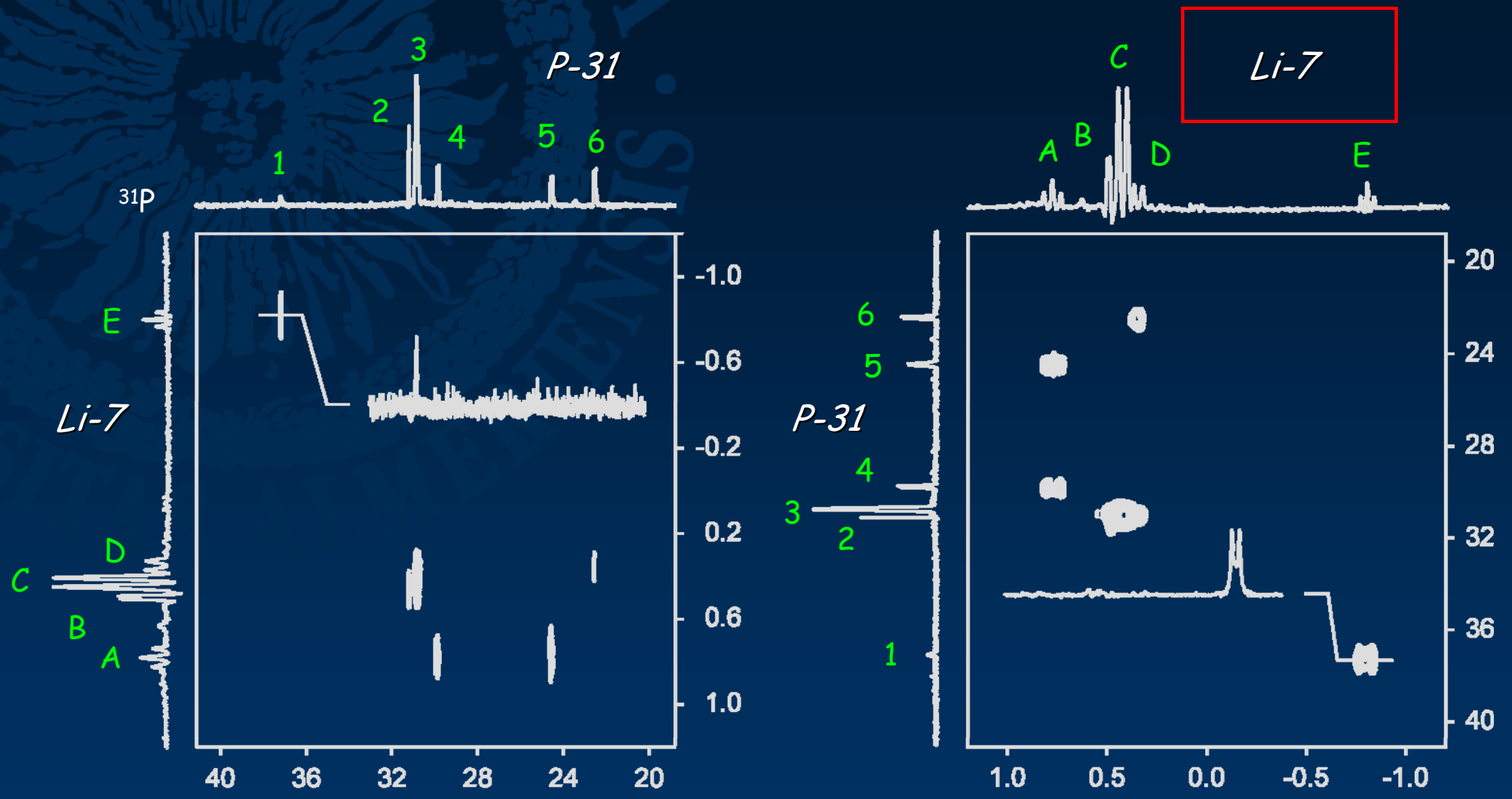


Experimental time = 2 h
S/N (cross-peak 1-E) = 300 (15 times more sensitive)

Chem. Commun. **2007**, 1142

^{31}P- vs ^{7}Li-detected HMQC NMR, -100 °C, 0.1 M, Et_2O-d_{10}

Lithium-7 detection !!



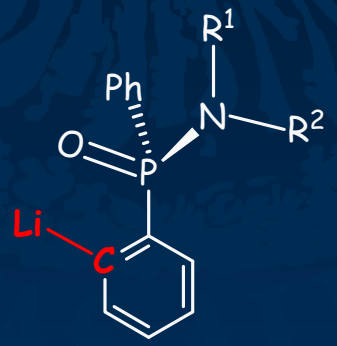
Experimental time = 1 h
S/N (cross-peak 1-E) = 20
20 x factor = 70

Why applying a correcting factor of 3.5 ?

Experimental time = 1 h
S/N (cross-peak 1-E) = 300

Chem. Commun. **2007**, 1142

PGSE Diffusion NMR

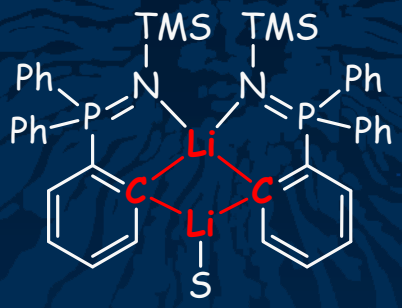


SOLUTION STRUCTURE ??

Multinuclear NMR

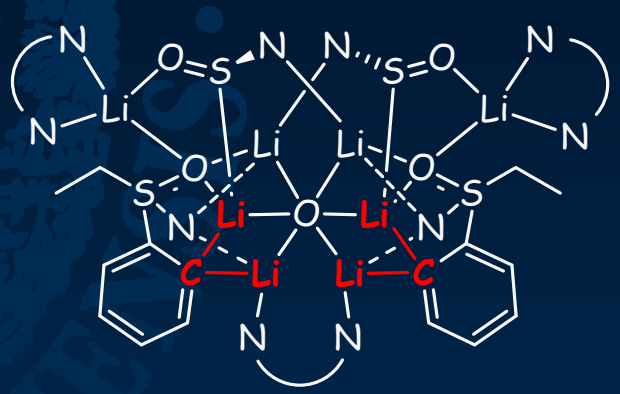
X/Y Shift Correlation

Any precedents ??

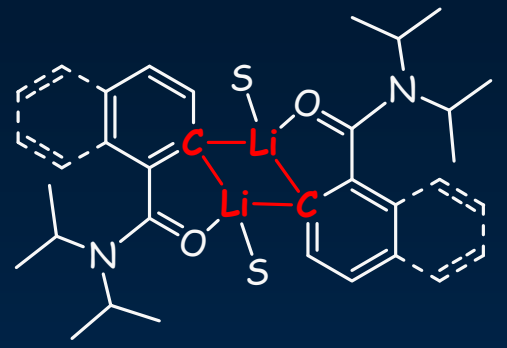


Stalke (*Angew* 1995)

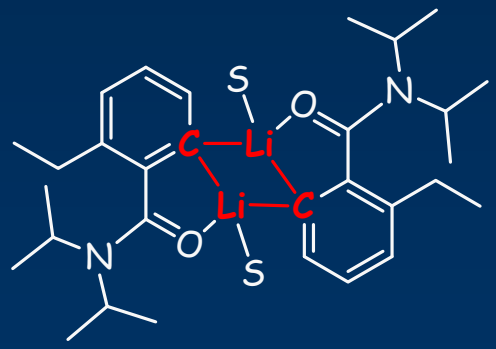
δ $(^{13}C)_{Li}$ = ~ 195 ppm



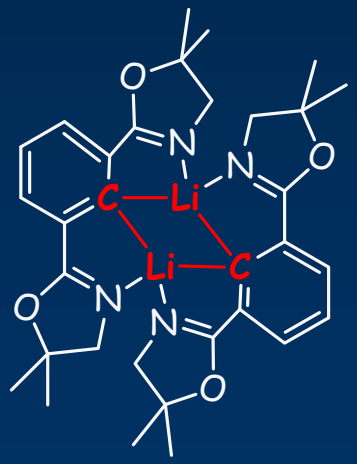
Muller (*Helvetica* 1997)



Clayden (*Angew* 2001)

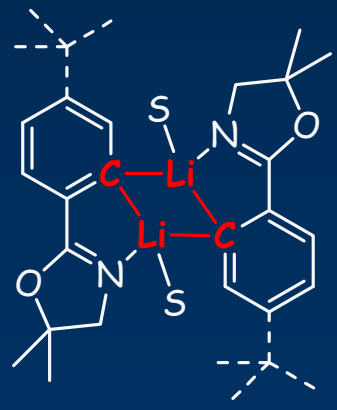


Clayden (*Angew* 2004)



Van Koten (*Organometallics* 2005)

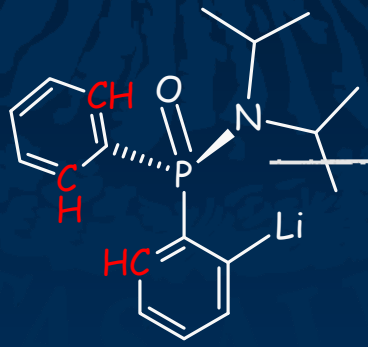
δ $(^{13}C)_{Li}$ = ~ 197 ppm

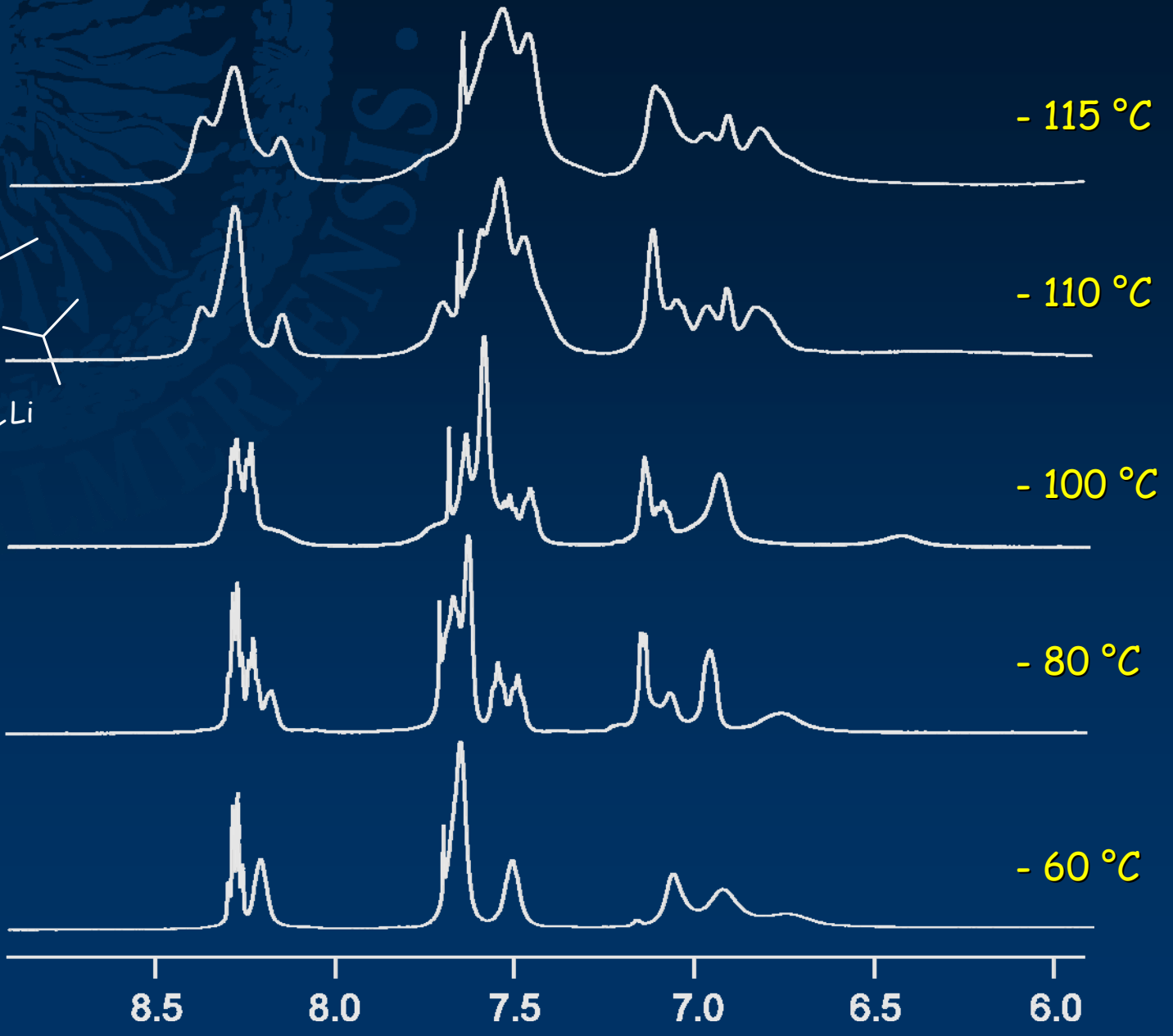


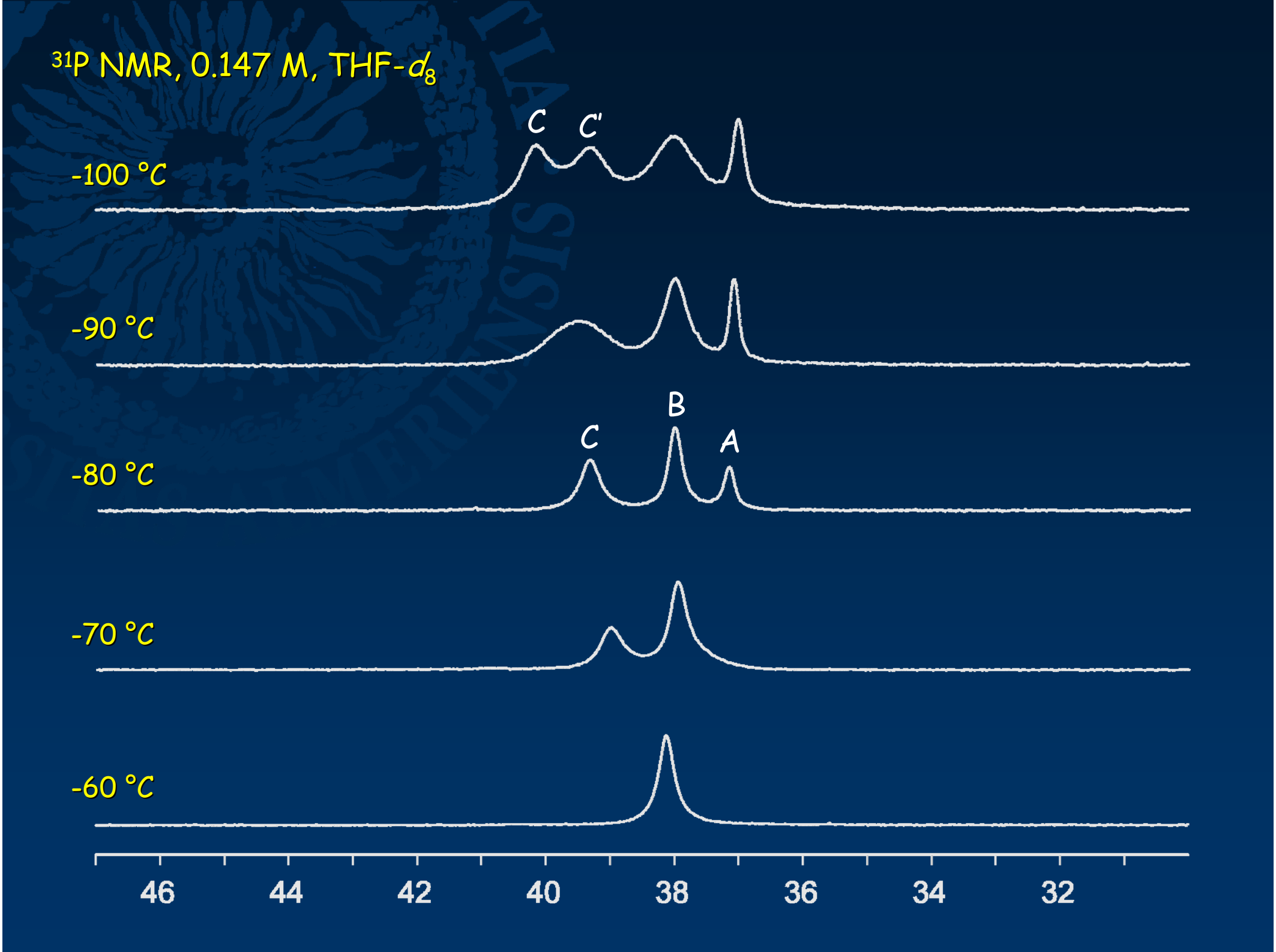
Reich (*Organometallics* 2006)

δ $(^{13}C)_{Li}$ = ~ 195 ppm

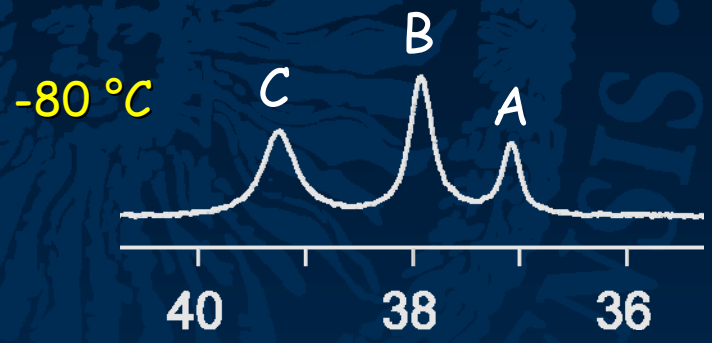
^{1}H NMR, 0.147 M, THF-d_8

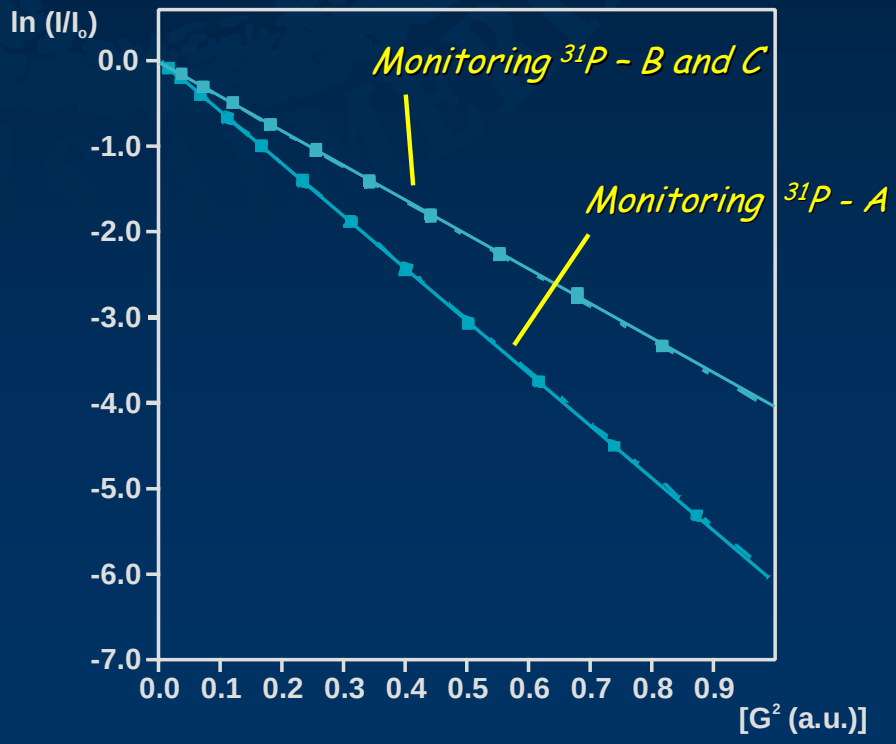





^{31}P NMR, 0.147 M, THF-d_8
-100 °C
C
C'
-90 °C
-80 °C
C
B
A
-70 °C
-60 °C
46
44
42
40
38
36
34
32

^{31}P PGSE (STE and SE) diffusion NMR, 0.147 M, -80 °C, THF-d_8



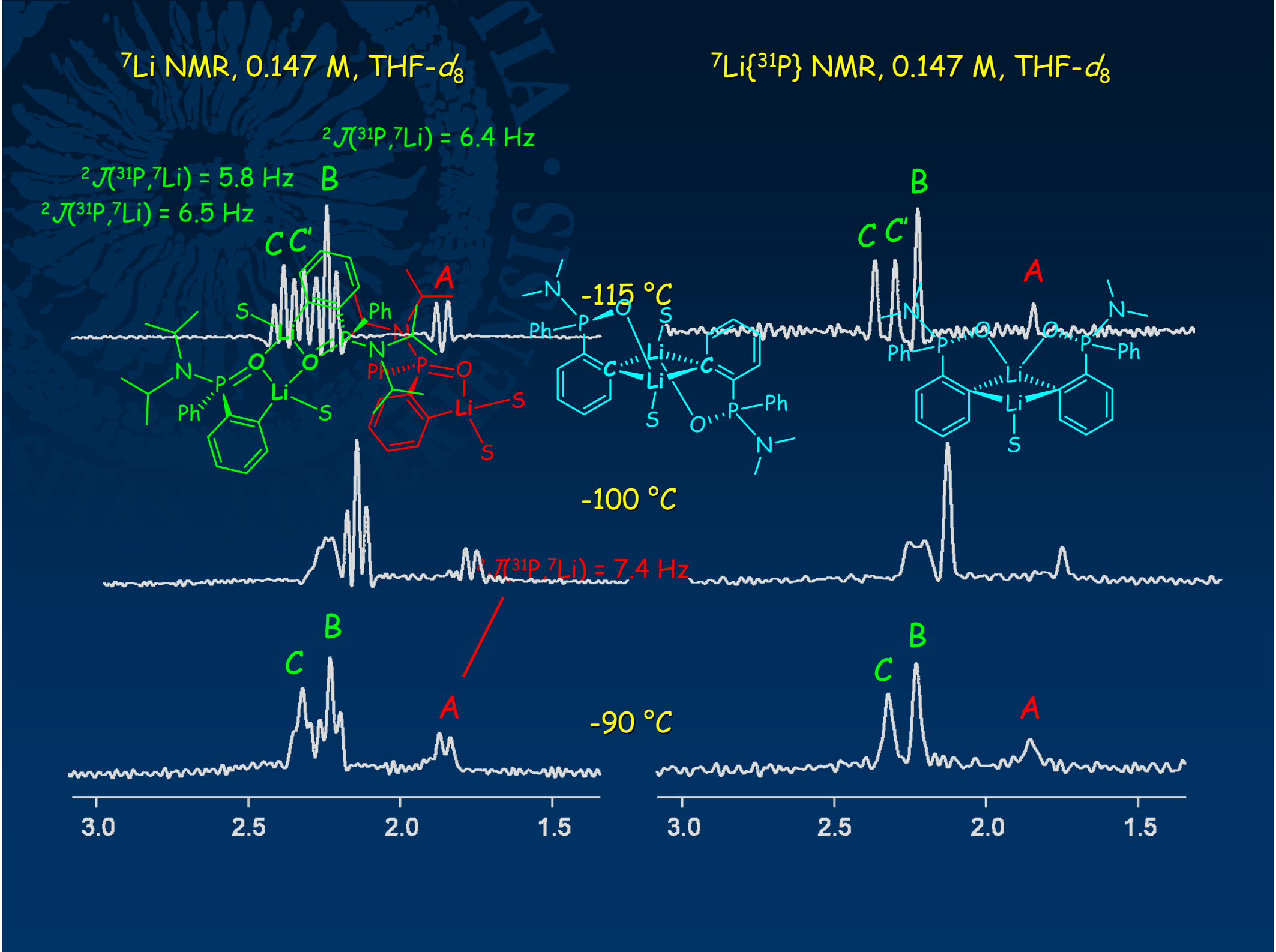


$D\ (^{31}P\text{-}A) = 0.301 \times 10^{-10}\ m^2\ s^{-1}$

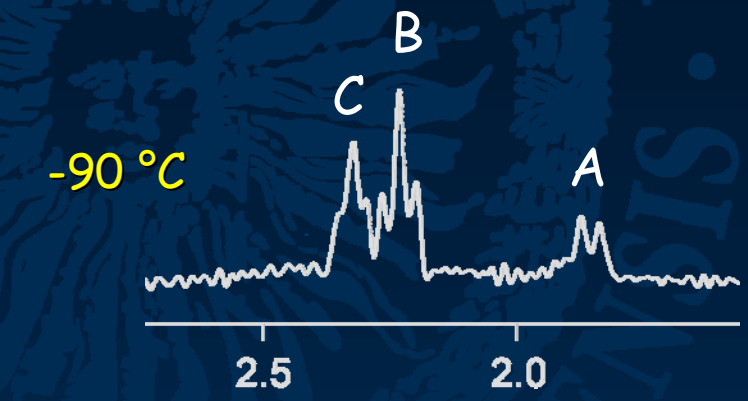
$r_H\ (^{31}P\text{-}A) = 5.1\ Å$

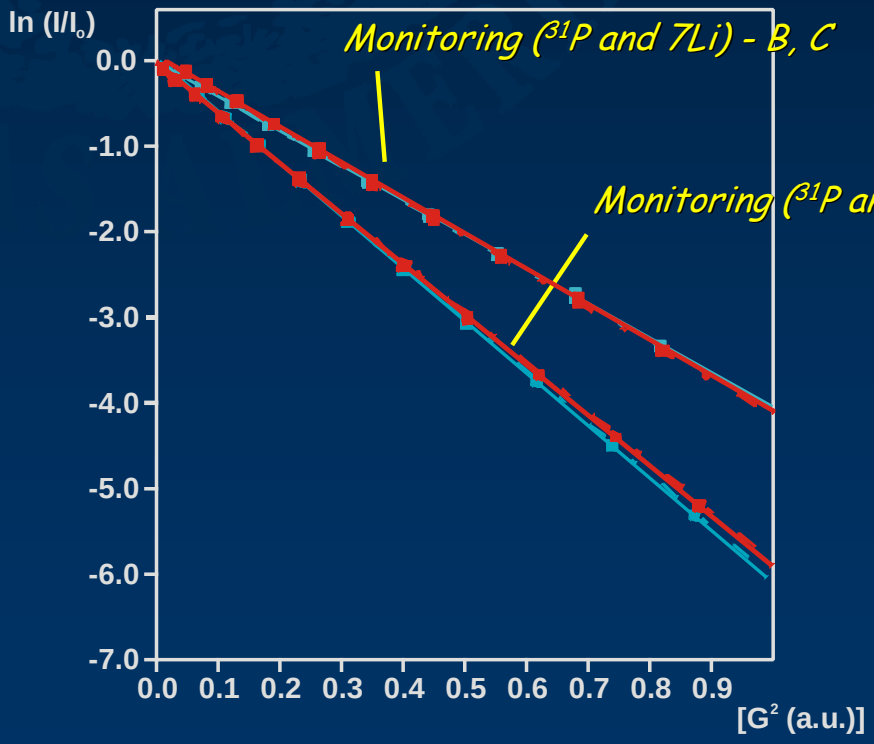
$D\ (^{31}P\text{-}B,C) = 0.233 \times 10^{-10}\ m^2\ s^{-1}$

$r_H\ (^{31}P\text{-}B,C) = 6.4\ Å$


^{7}Li NMR, 0.147 M, THF-d_8
^{7}Li{^{31}P} NMR, 0.147 M, THF-d_8
$^2J(^{31}P,^7Li)$ = 6.4 Hz
$^2J(^{31}P,^7Li)$ = 5.8 Hz
$^2J(^{31}P,^7Li)$ = 6.5 Hz
B
C C′
A
-115 °C
-100 °C
$^2J(^{31}P,^7Li)$ = 7.4 Hz
-90 °C
3.0
2.5
2.0
1.5

^{7}Li PGSE (STE) diffusion NMR, 0.147 M, -90 °C, THF-d_8





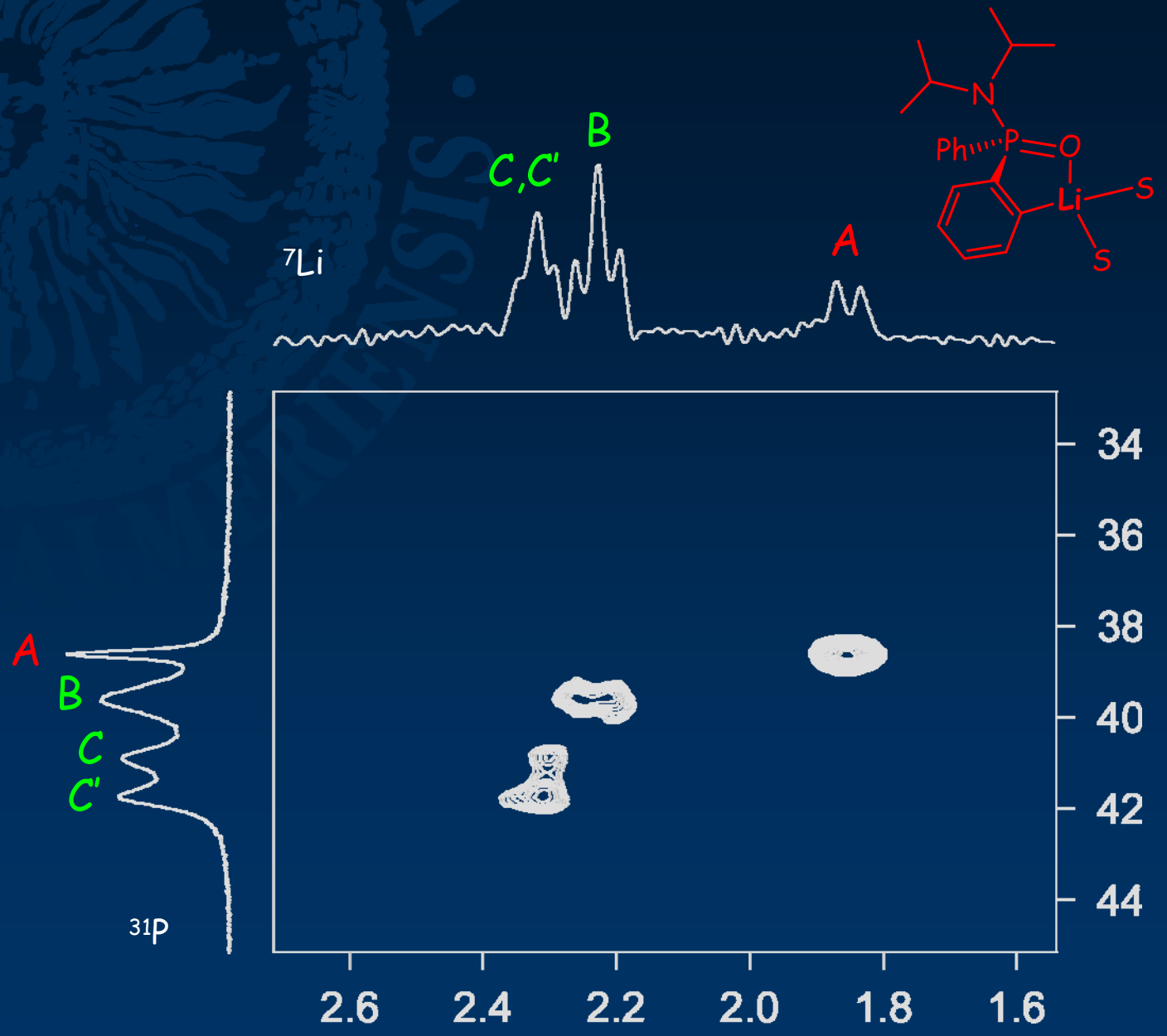
D (^{31}P-A) = 0.301 × 10^{-10} m^2 s^{-1}
D (^{7}Li-A) = 0.299 × 10^{-10} m^2 s^{-1}

r_H (^{31}P)-A = 5.1 Å
r_H (^{7}Li-A) = 5.1 Å

D (^{31}P-B,C) = 0.233 × 10^{-10} m^2 s^{-1}
D (^{7}Li-B,C) = 0.231 × 10^{-10} m^2 s^{-1}

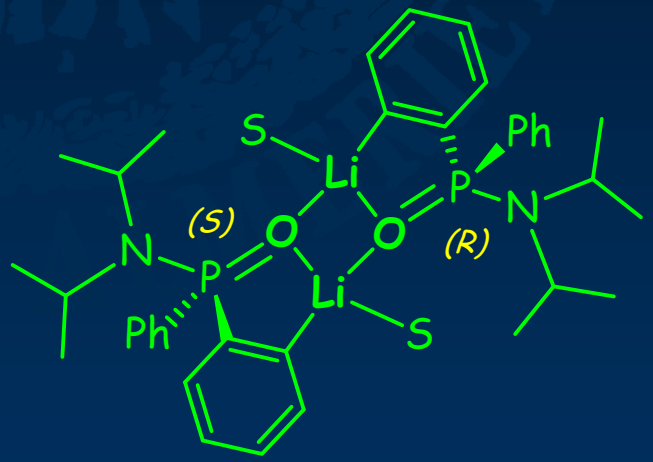
r_H (^{31}P-B,C) = 6.4 Å
r_H (^{7}Li-B,C) = 6.4 Å

^{7}Li,^{31}P HMQC NMR, -100 °C, 0.147 M, THF-d_8



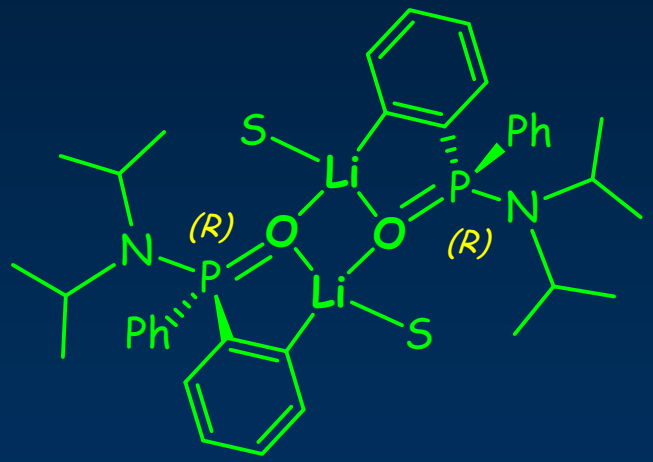
Dimers … , but … why more than one ??

B



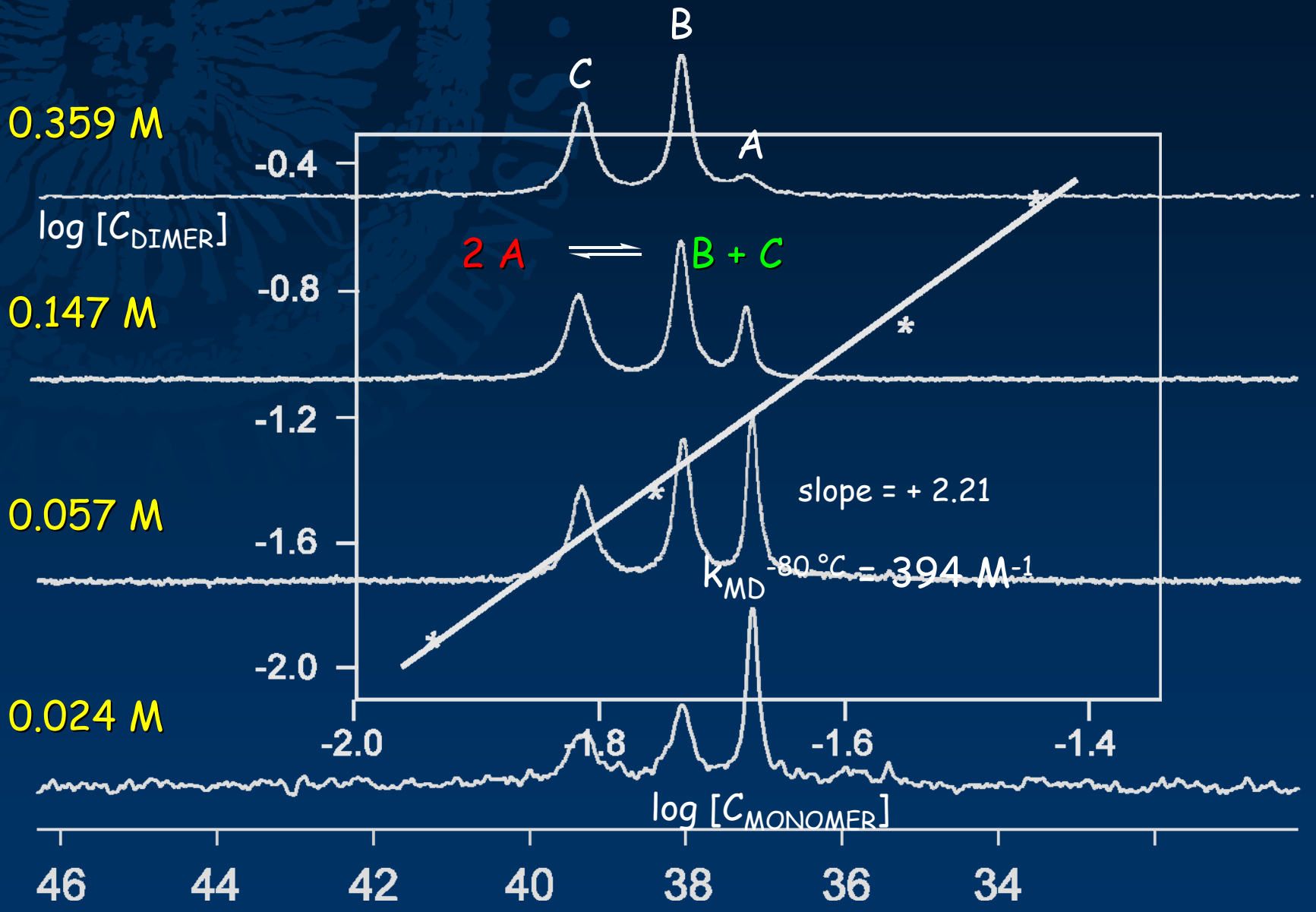
(R_P*, S_P*)

C,C'

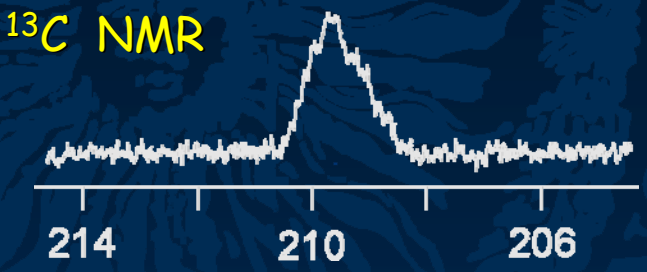


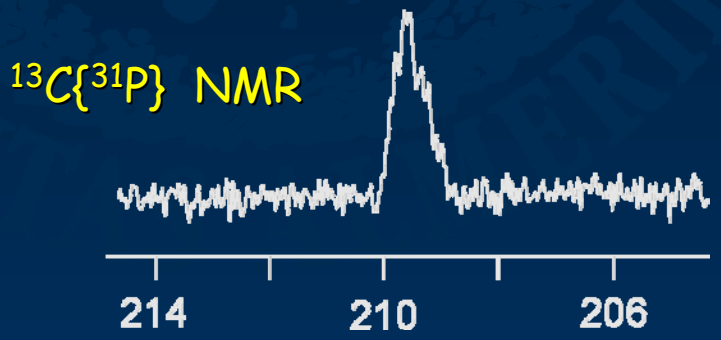
(R_P*, R_P*)

^{31}P NMR, -80 °C, as a function of concentration



^{13}C NMR, -100 °C, 0.147 M, THF-d_8

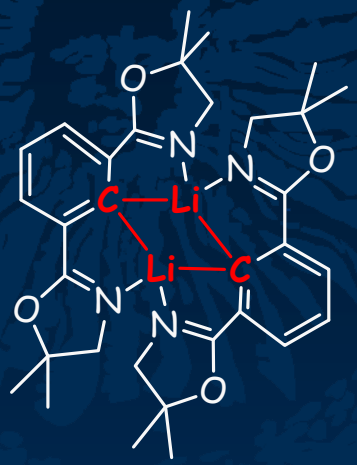




~ 209 ppm

200 150 100 50 0

^{13}C NMR comparison, THF-d_8

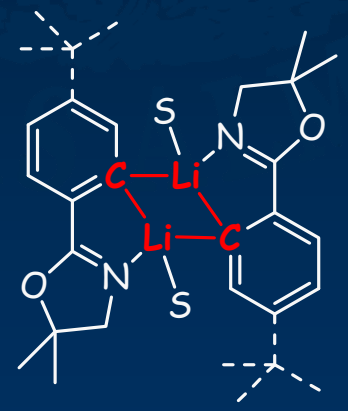


DIMERS

$\delta\ (^{13}C)_{Li}$ = ~ 197 ppm

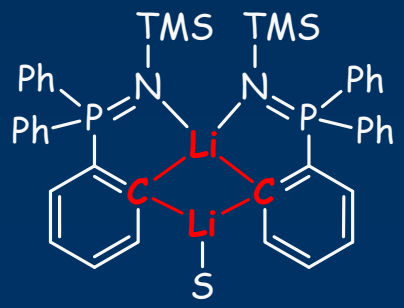
MONOMERS

$\delta\ (^{13}C)_{Li}$ = ~ 207 ppm

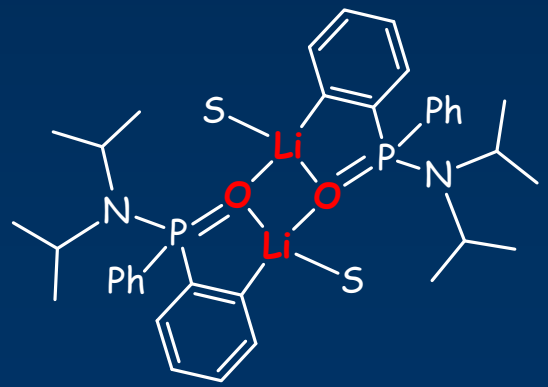


$\delta\ (^{13}C)_{Li}$ = ~ 195 ppm

$\delta\ (^{13}C)_{Li}$ = ~ 210 ppm



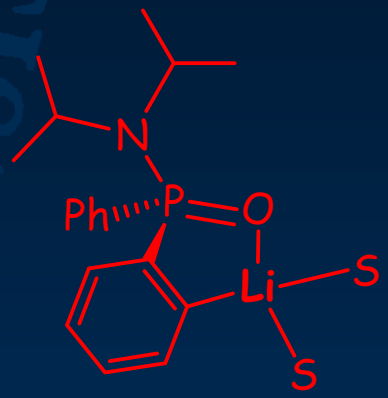
$\delta\ (^{13}C)_{Li}$ = ~ 195 ppm



$\delta\ (^{13}C)_{Li}$ = ~ 209.2 ppm

But… how do they exchange ?? **EXchange S**pectroscop**Y**

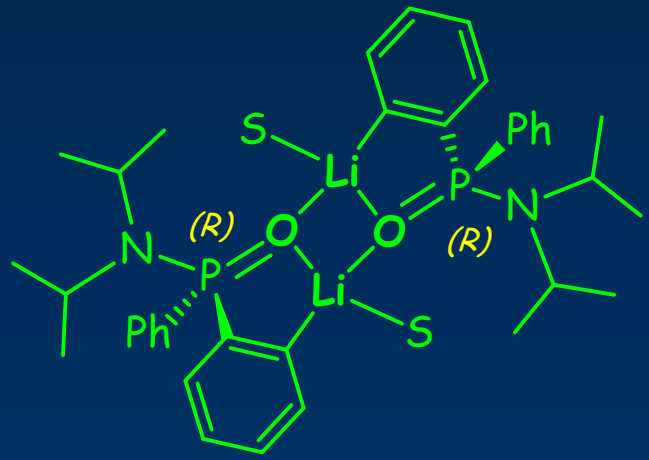
A



B

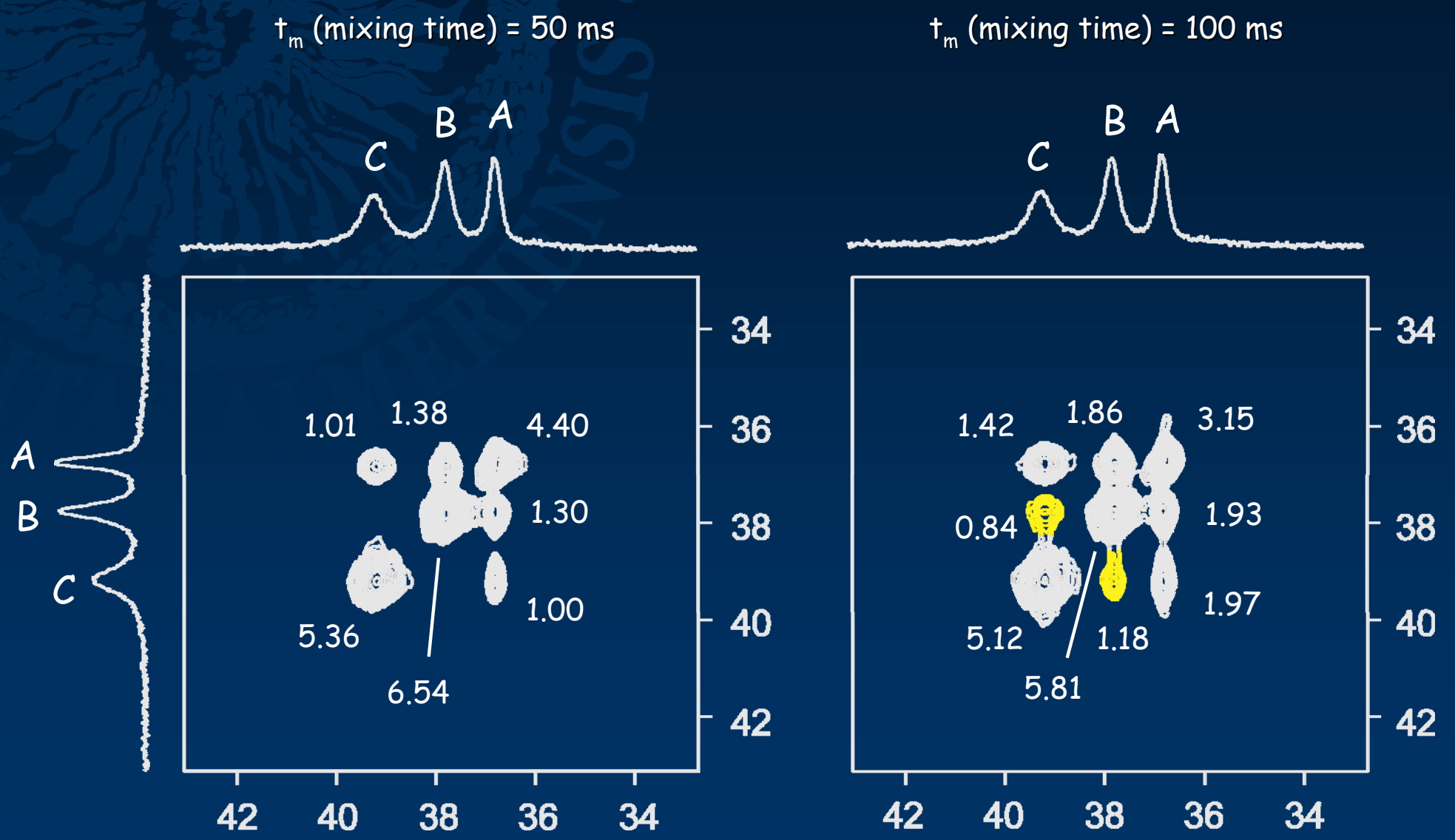
(R_P^*, S_P^*)

C

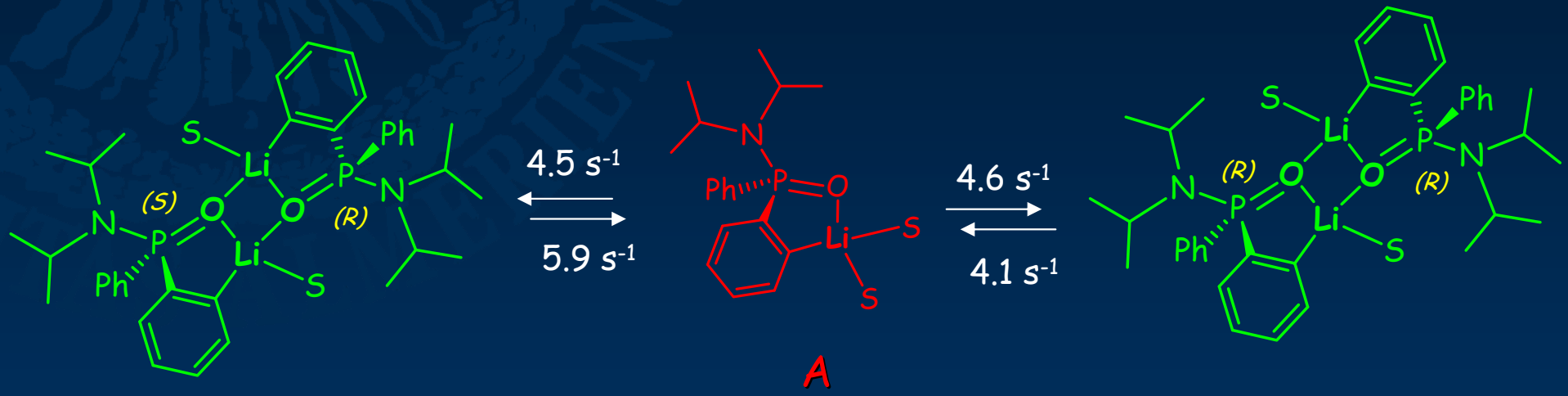


(R_P^*, R_P^*)

$^{31}P,^{31}P$ EXSY NMR, -80 °C, 0.057 M, THF-d_8



EXSY studies !!



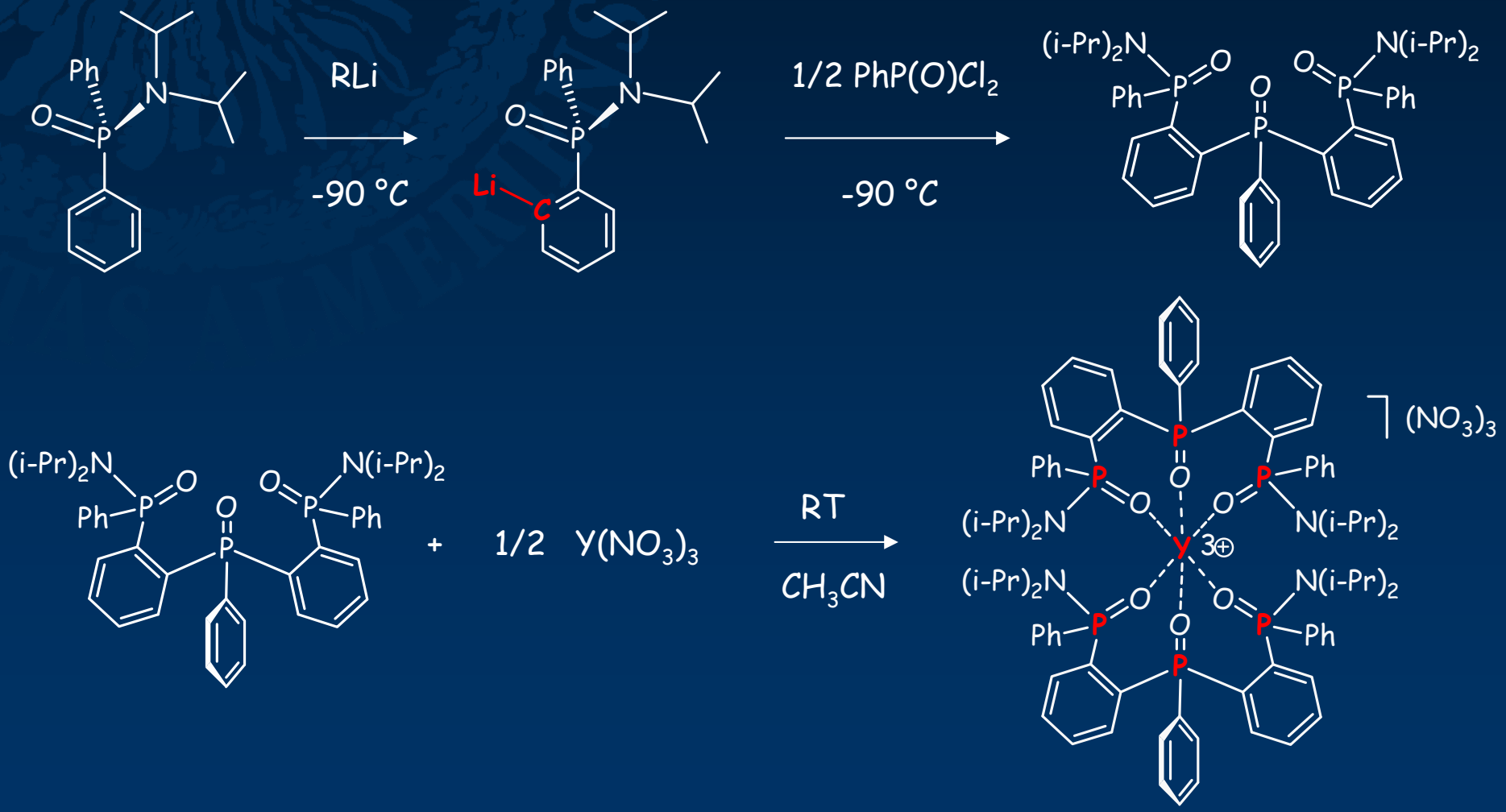
B (R_P^*, S_P^*)

C (R_P^*, R_P^*)

The two dimers are in exchange only THROUGH the monomer !!
And not THROUGH higher aggregations states and/or triple ions !!

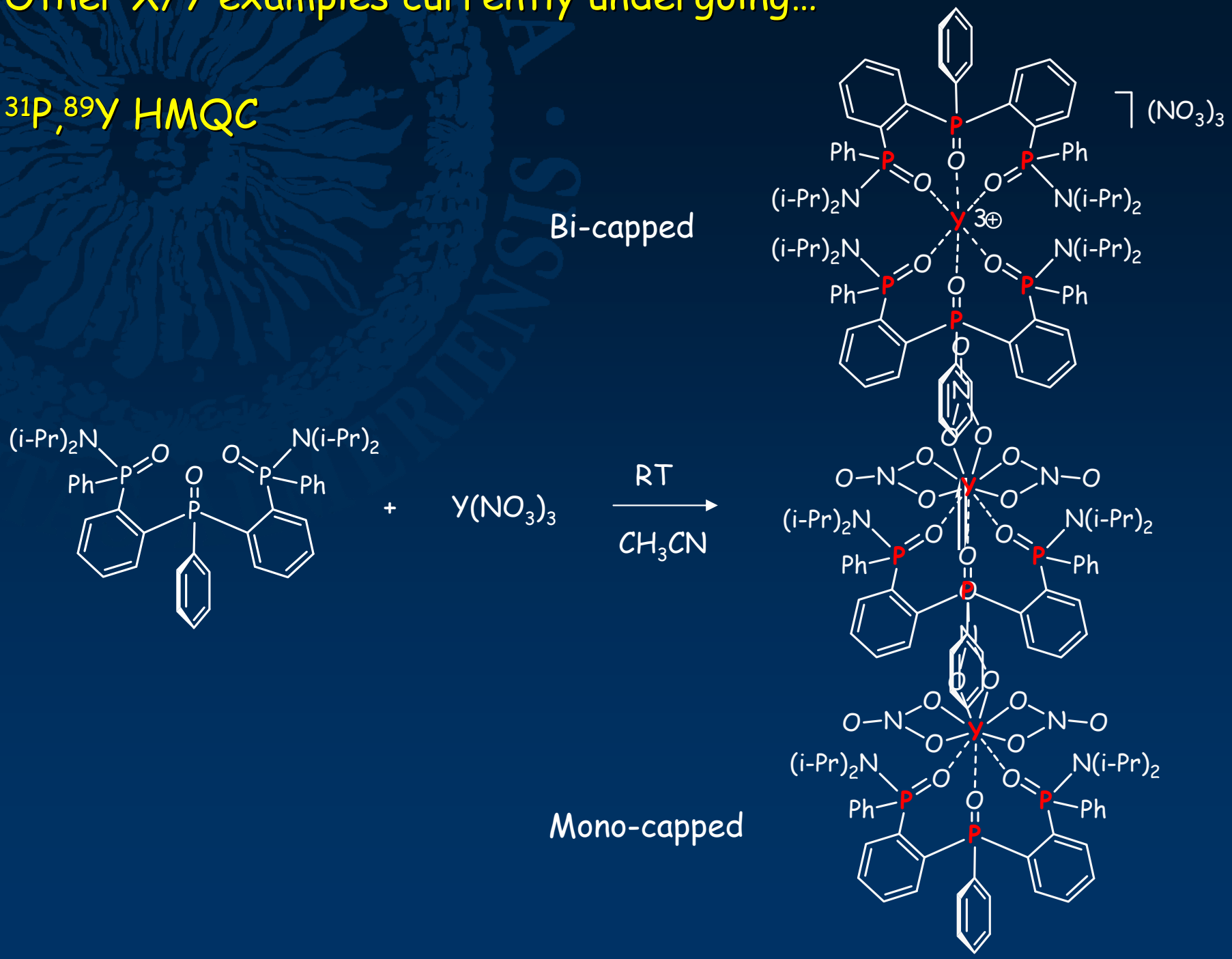
Other X/Y examples currently undergoing…

^{31}P,^{89}Y HMQC



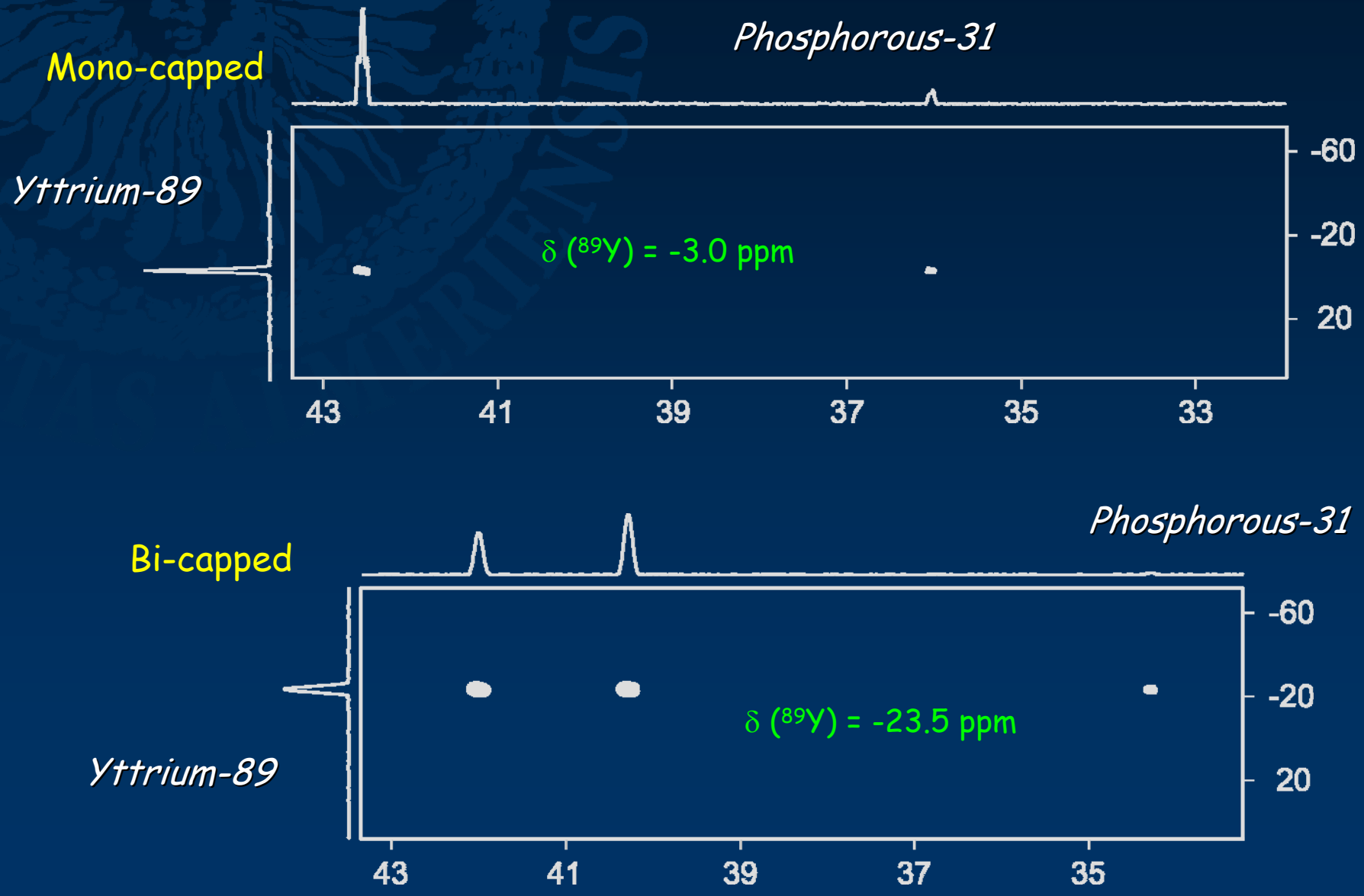
Other X/Y examples currently undergoing…

^{31}P, ^{89}Y HMQC



Other X/Y examples currently undergoing…

$^{31}P, ^{89}Y$ HMQC



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Cristinel Popovici
(Almeria)

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Dr. Heinz Ruegger
(Zurich)

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Centro Nacional de Investigaciones Oncológicas

Unprecedented Structures driven by the Phosphinamide Linkage – A Multinuclear NMR Touch

Ignacio Fernández

Universidad de Almería (Spain)

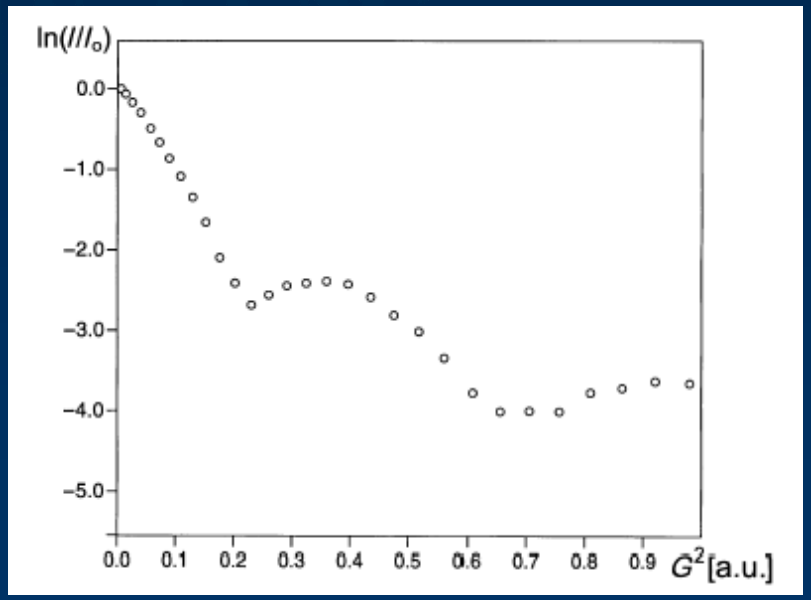
EURACT NMR
KARLSRUHE 2010

Convection: A quite familiar problem on RLi diffusion

Convection introduces a cosine modulation on signal attenuation. The resulting effect is governed by

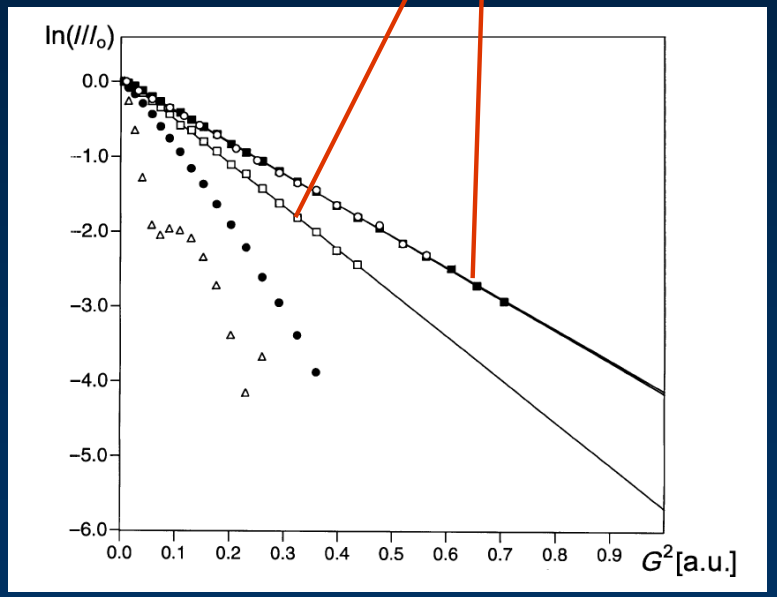
Flow rate

$$I(2\tau)/I_o \propto \cos(\gamma G\delta \upsilon \Delta) \quad \exp -\left[(\gamma G\delta)^2 D(\Delta - \delta/3)\right]$$



In laminar flow conditions where (u^2 x D) << D and d << D (most common case), the apparent diffusion coefficient appears

$$D_{app} = D + \frac{\upsilon^2 \Delta}{2}$$



Wrong D values

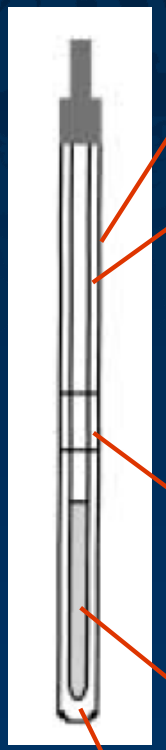
Langmuir **2000**, *16*, 7548.

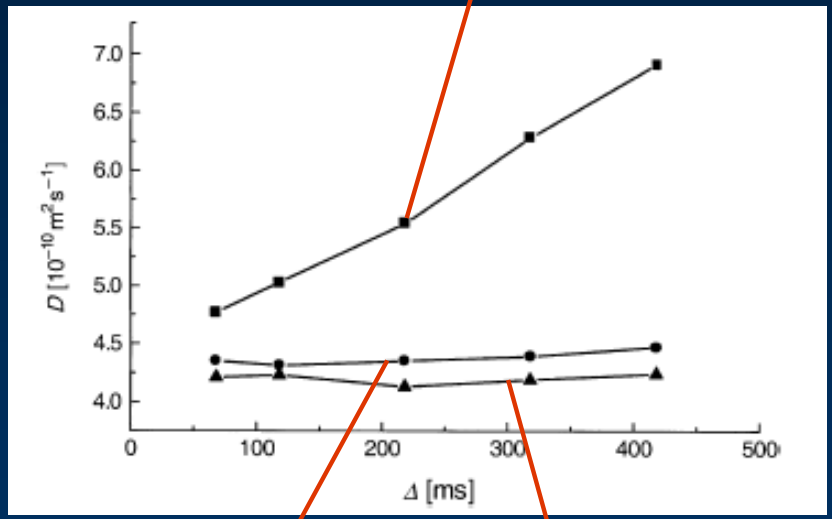
Helv. Chim. Acta **2003**, *86*, 2364.

Convection: A quite familiar problem on RLi measurements

1) Double stimulated echo sequences
2) Spinning
3) Concentric tubes

$$D_{app} = D + \frac{\upsilon^2 \Delta}{2}$$

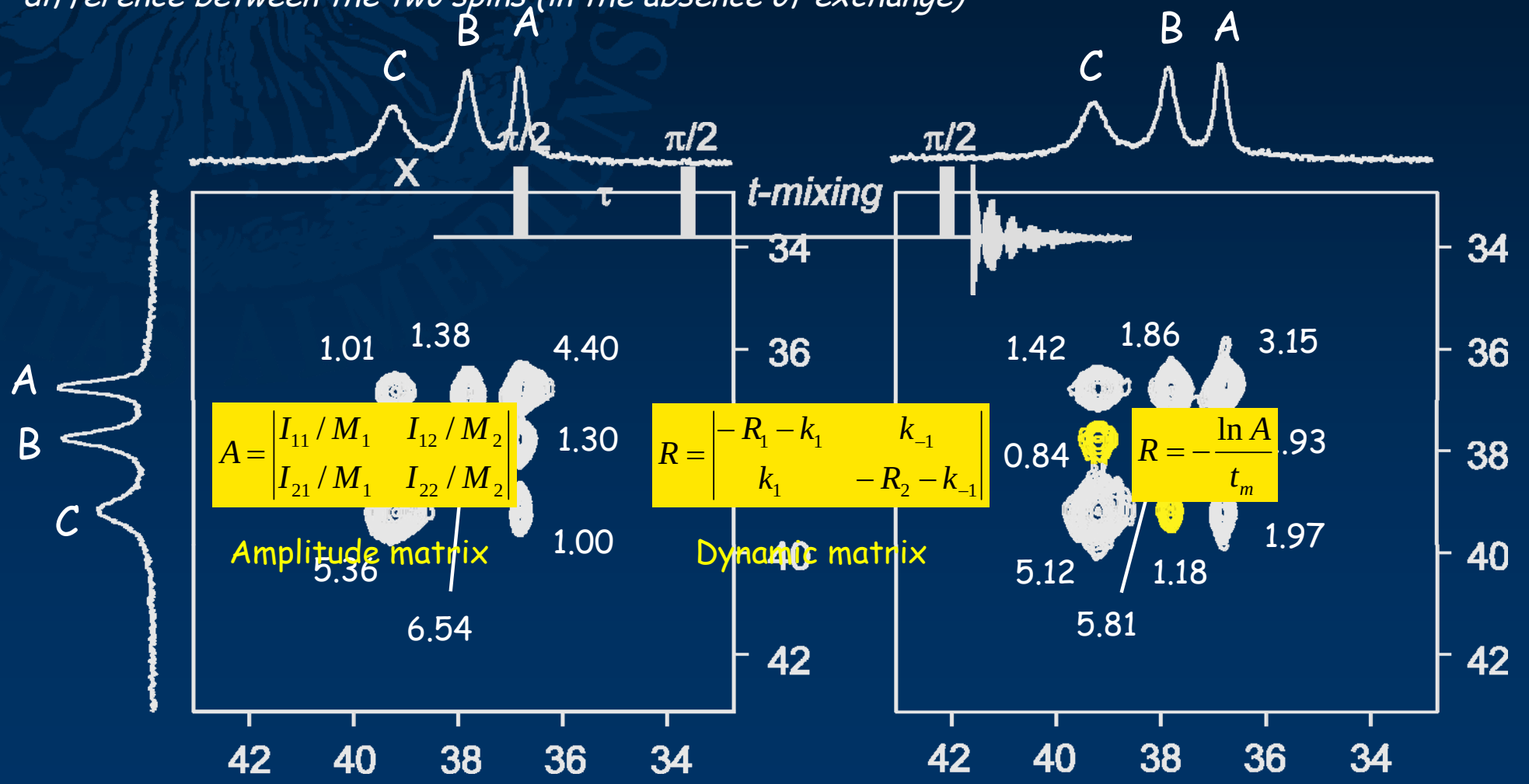




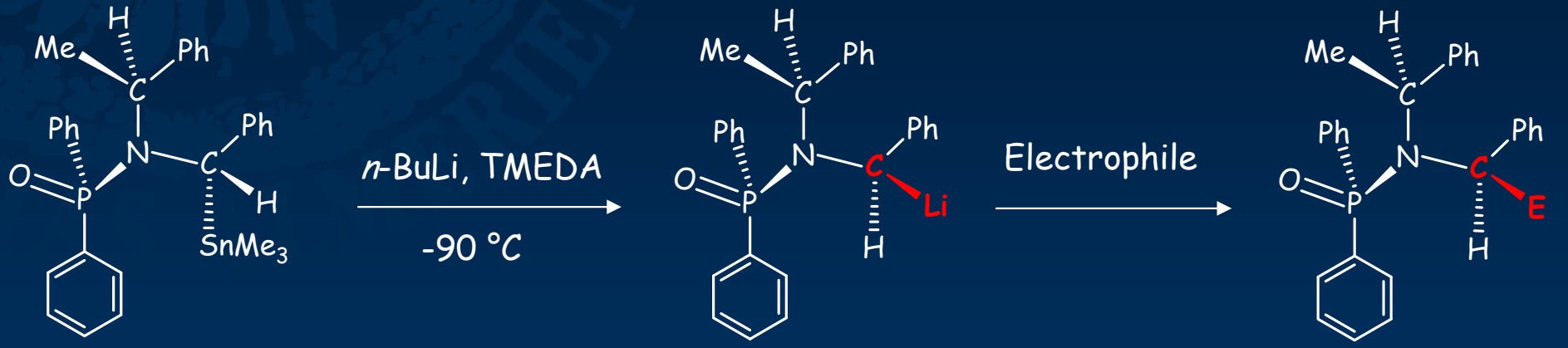
Helv. Chim. Acta **2003**, *86*, 2364.

$^{31}P, ^{31}P$ EXSY NMR, -80 °C, 0.057 M, THF-d_8

*The 2D **EXSY** technique provides off-diagonal responses for spins which exchange slowly with one another. The EXSY method is useful for showing exchange when the rate of the exchange is greater than or of the same order as the T1 relaxation rate (1/T1) but less than the frequency difference between the two spins (in the absence of exchange)*



1) Diethyl Ether - C_α metalation – Double Asymmetric Induction

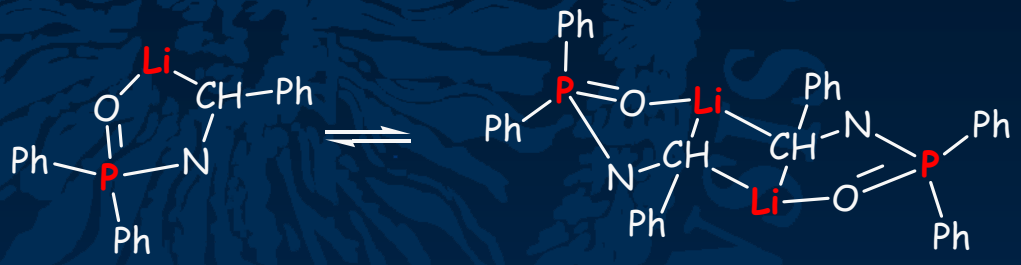


(*S*,*R*)

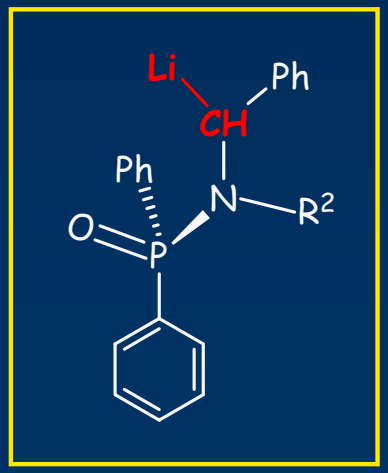
E = RX, RCHO
RHC=CH(O)R

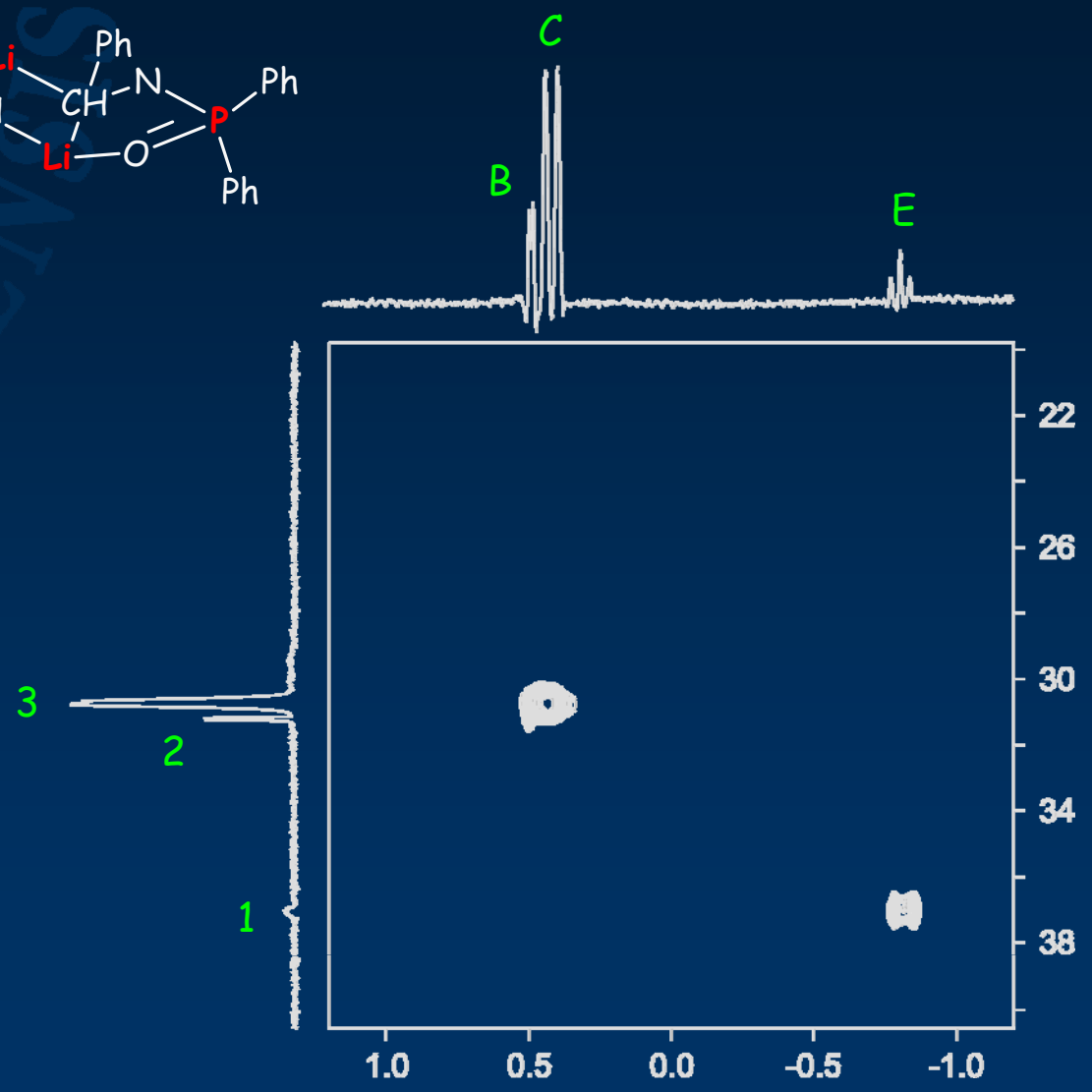
Org. Lett. **2008**, 10, 3195

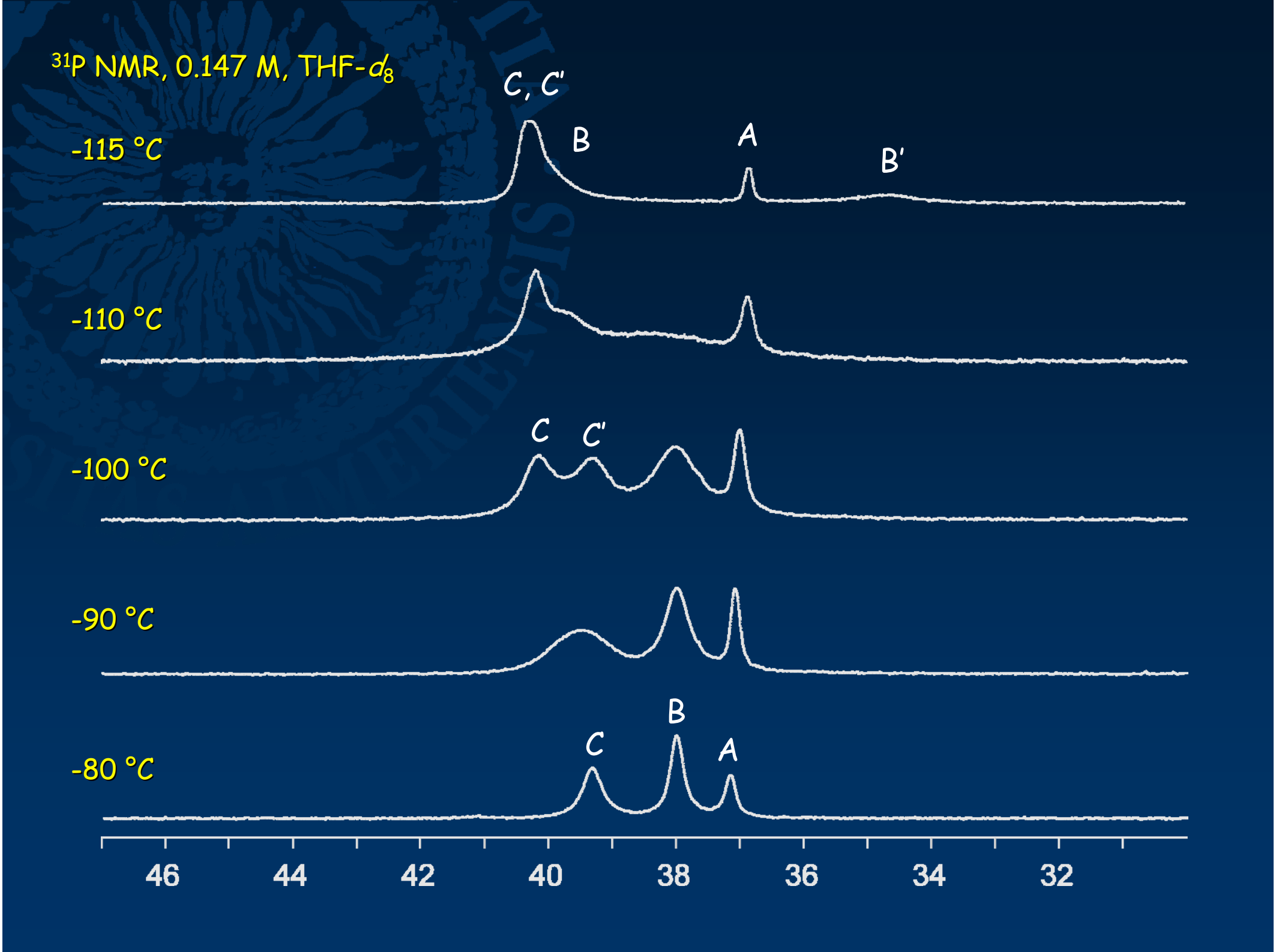
Multinuclear NMR: X/Y Shift Correlation



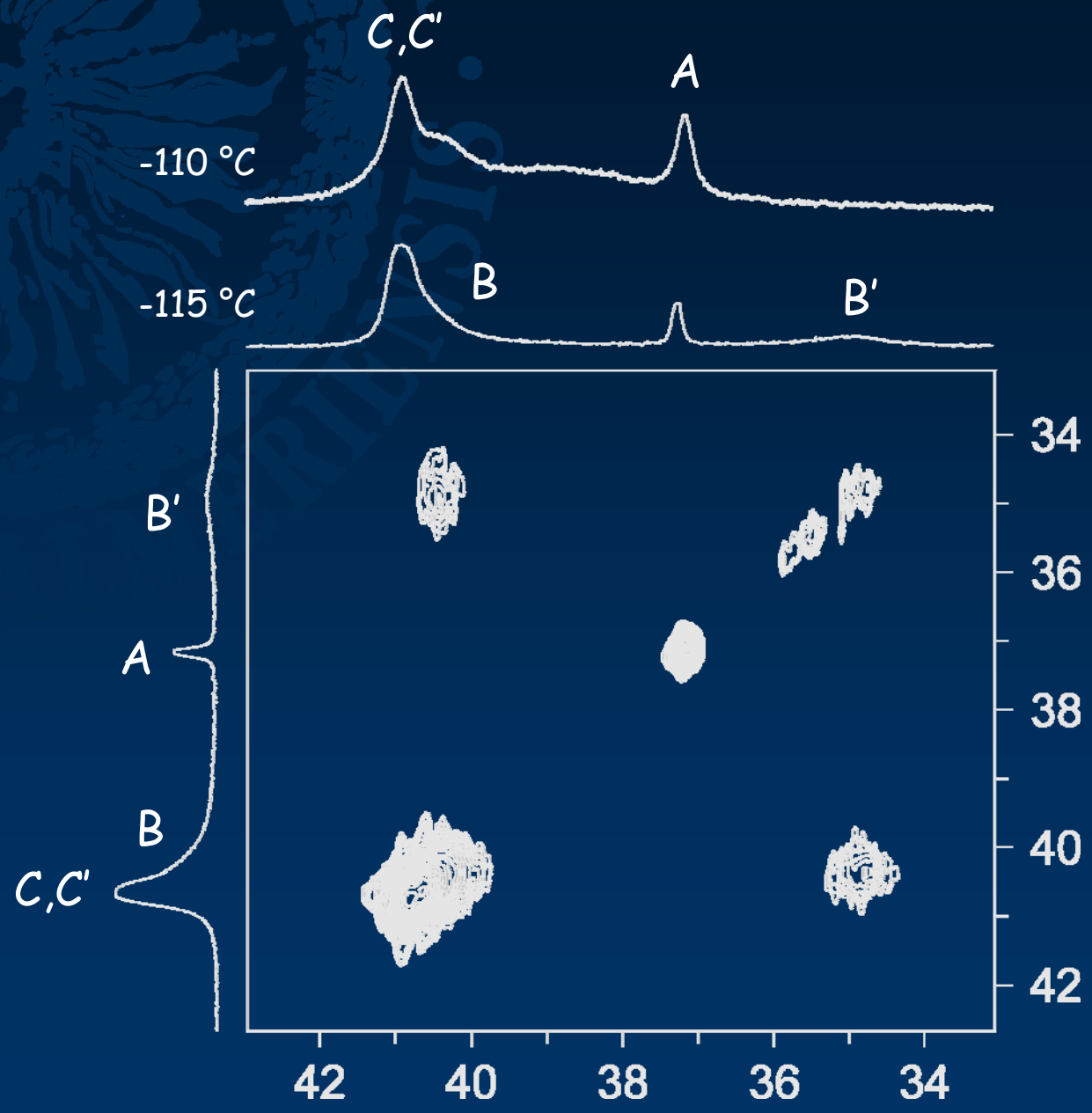
Monomer-Dimer






^{31}P NMR, 0.147 M, THF-d_8
-115 °C
C, C′
B
A
B′
-110 °C
-100 °C
C
C′
-90 °C
-80 °C
B
C
A
46
44
42
40
38
36
34
32

$^{31}P,^{31}P$ EXSY NMR -115 °C, 0.147 M, THF-d_8



$^{31}P,^{31}P$ EXSY NMR, -80 °C, 0.057 M, THF-d_8

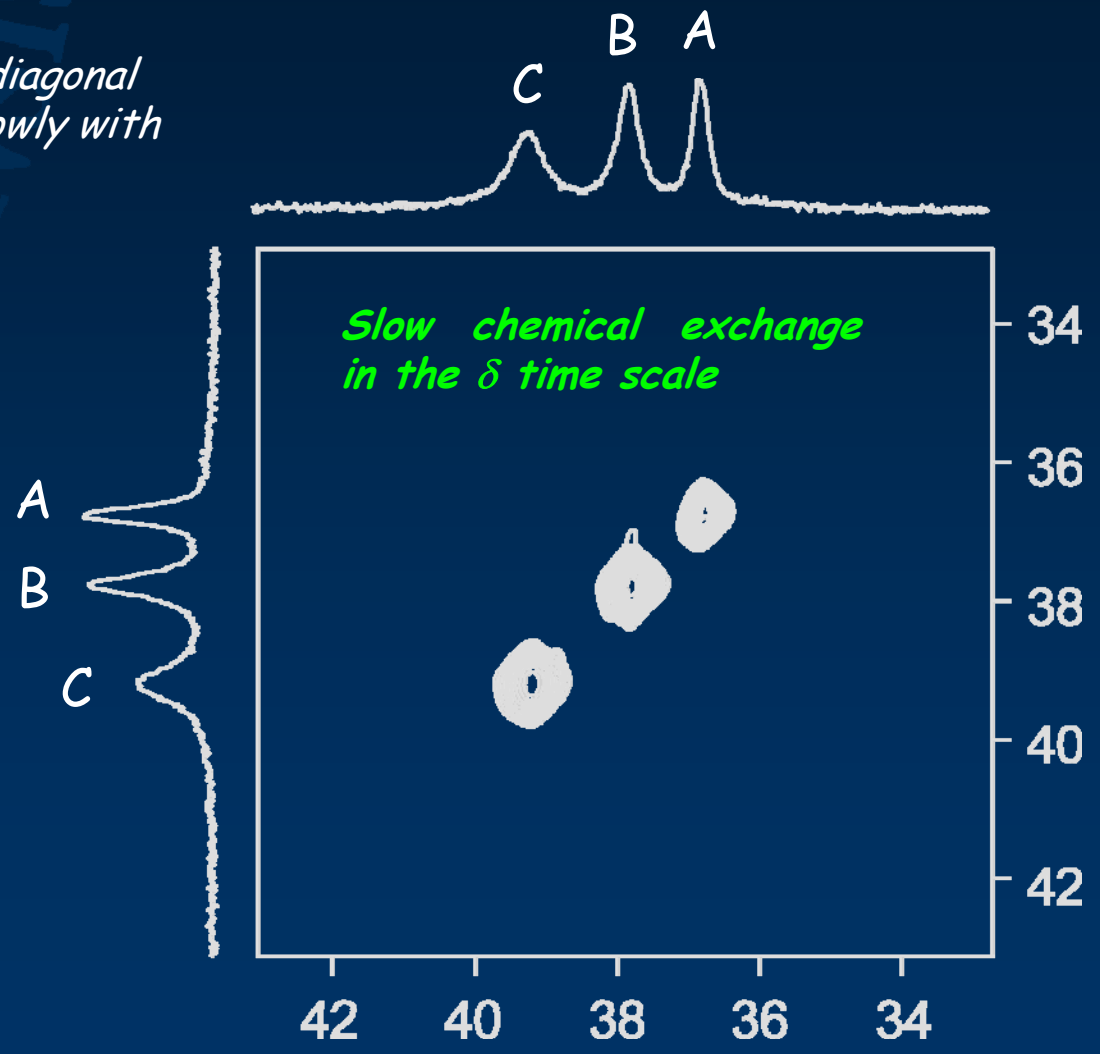
t_m (mixing time) = 2.4 ms (instrument limit)

*The 2D **EXSY** technique provides off-diagonal responses for spins which exchange slowly with one another.*

$$A = \begin{vmatrix} I_{11}/M_1 & I_{12}/M_2 \\ I_{21}/M_1 & I_{22}/M_2 \end{vmatrix}$$

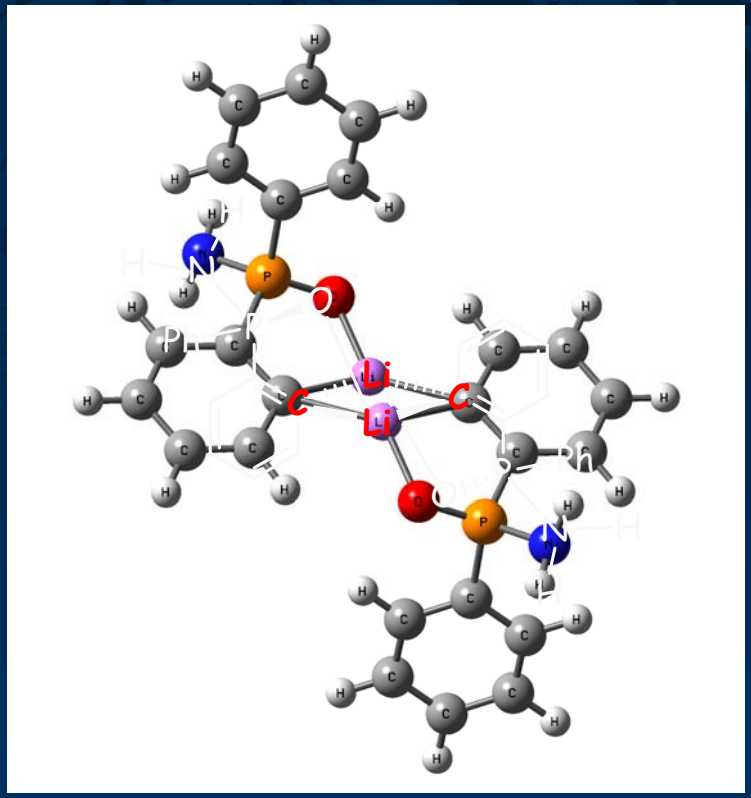
$$R = \begin{vmatrix} -R_1 - k_1 & k_{-1} \\ k_1 & -R_2 - k_{-1} \end{vmatrix}$$

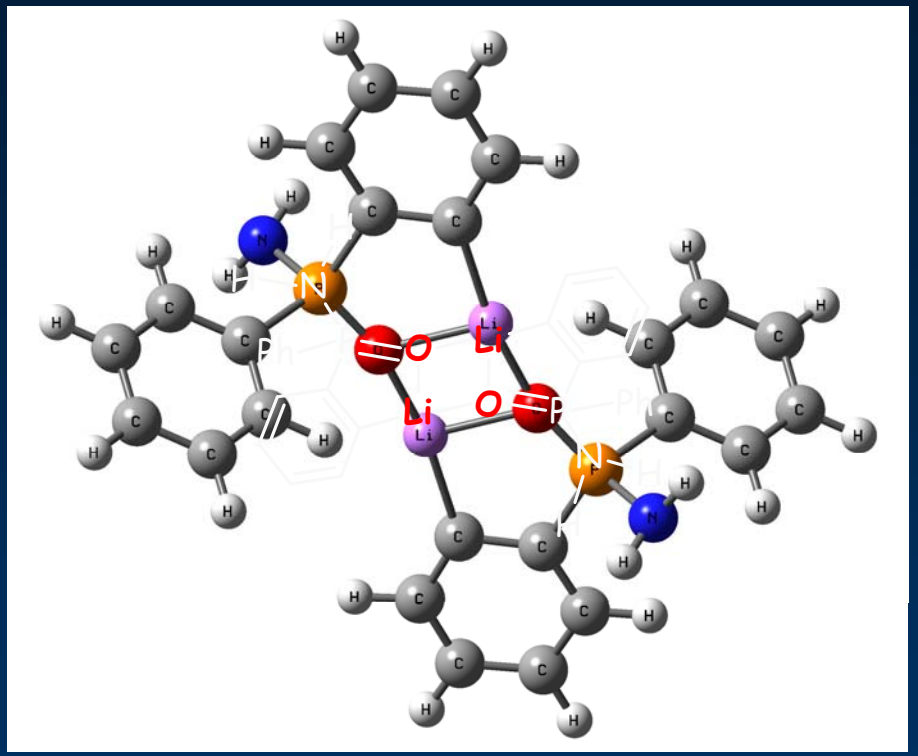
$$R = -\frac{\ln A}{t_m}$$



Calculations

Optimized geometry of both complexes at B3LYP/6-311+G(2d,p) level of theory. (C_i symmetry)



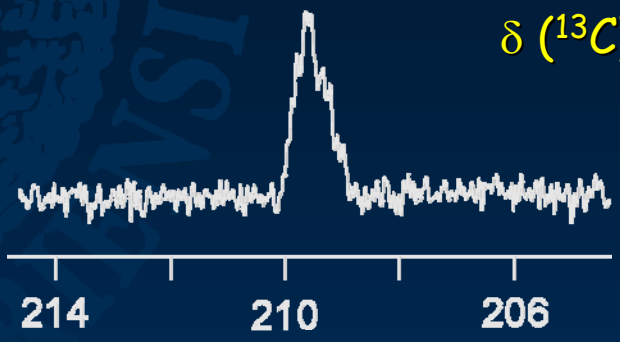


E_{rel} = + 5.8 kcal/mol

E_{rel} = + 0 kcal/mol

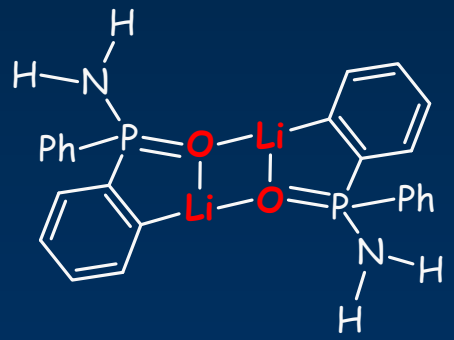
NMR and Calculations

$^{13}C\{^{31}P\}$ NMR, -100 °C



$\delta\ (^{13}C)_{exp}$ = ~ 209 ppm

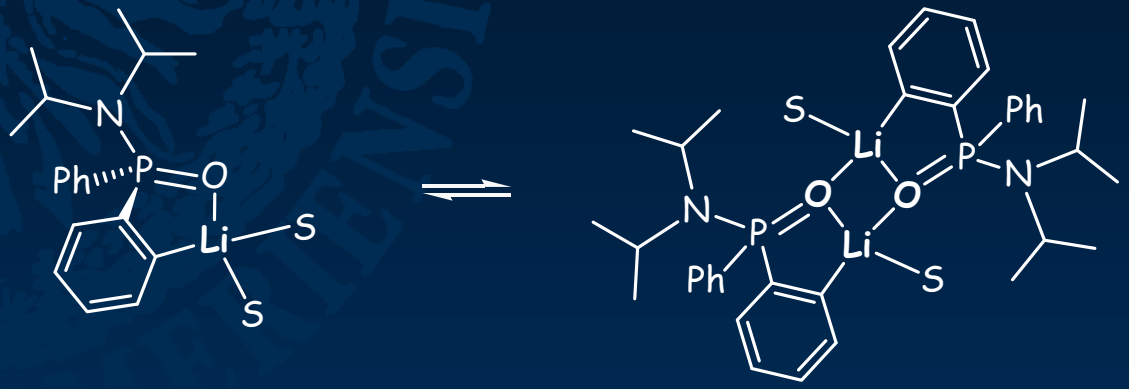
$\delta\ (^{13}C)$ = 194.0 ppm



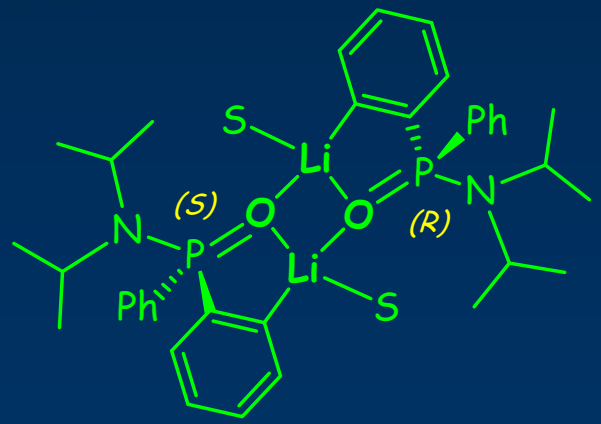
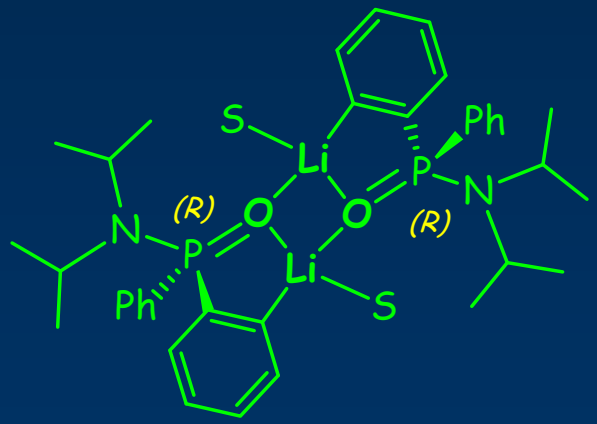
$\delta\ (^{13}C)$ = 208.0 ppm

^{13}C NMR GIAO chemical shift (referred to TMS) of the lithiated carbon in both complexes. Calculations at B3LYP/6-311+G(2d,p) level of theory.

So then … dimers based on Li_2O_2 cores !



B



C