# NMR on Organocopper Compounds

**EURACT - NMR**
**Karlsruhe, 27th January 2010**

**Ruth M. Gschwind**

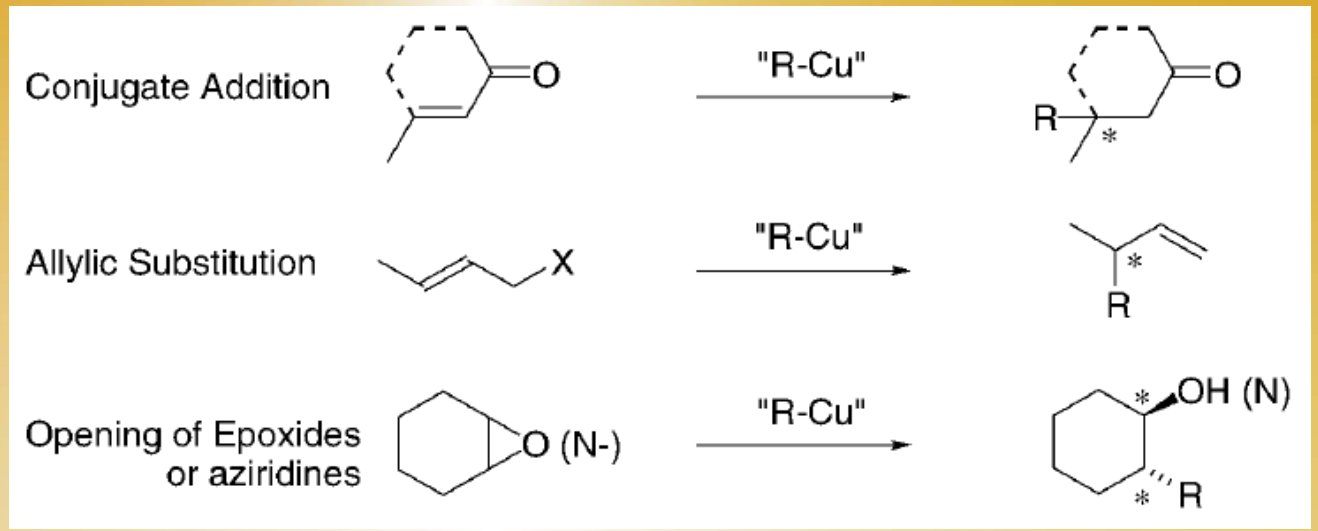
# Copper

Biology: copper metalloenzymes
- oxygen transport proteins
- electron transfer proteins

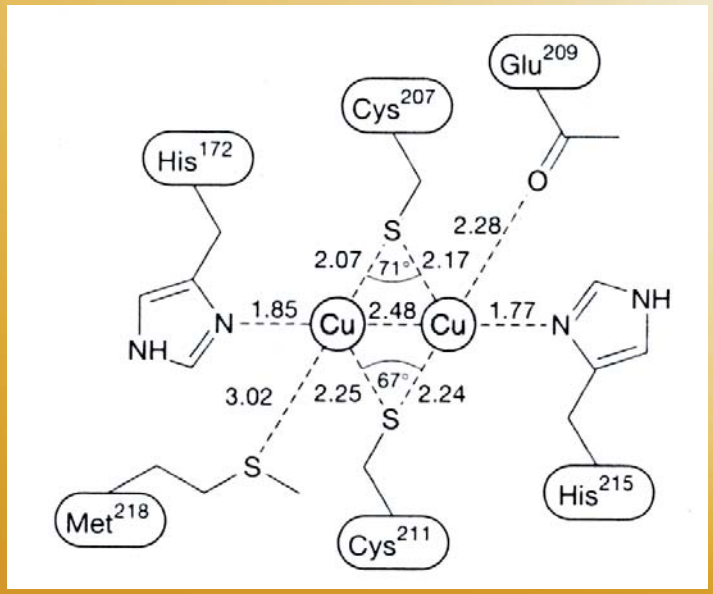
Organic Synthesis: main coupling reactions:
- Ullmann reaction
- Sandmeyer reaction
- Glaser reaction

main diastereoselective reactions:
- organocuprates: Addition and substitution reactions

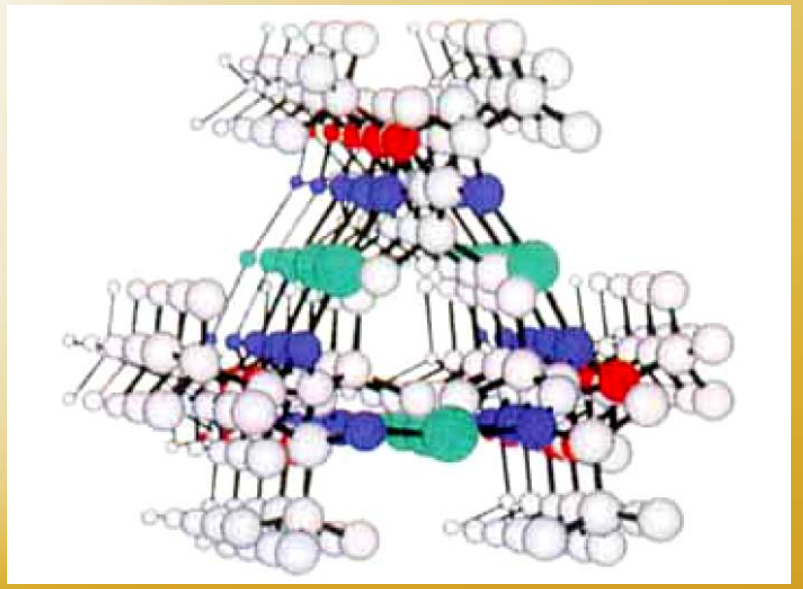
main enantioselective reactions (often catalytic):



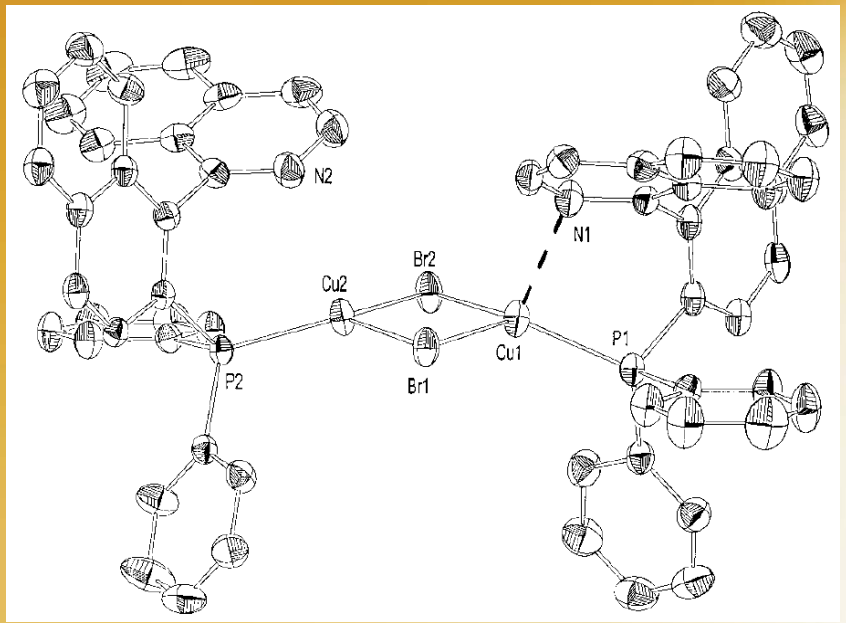
# Supramolecular Structures with Transition Metals e.g. Cu



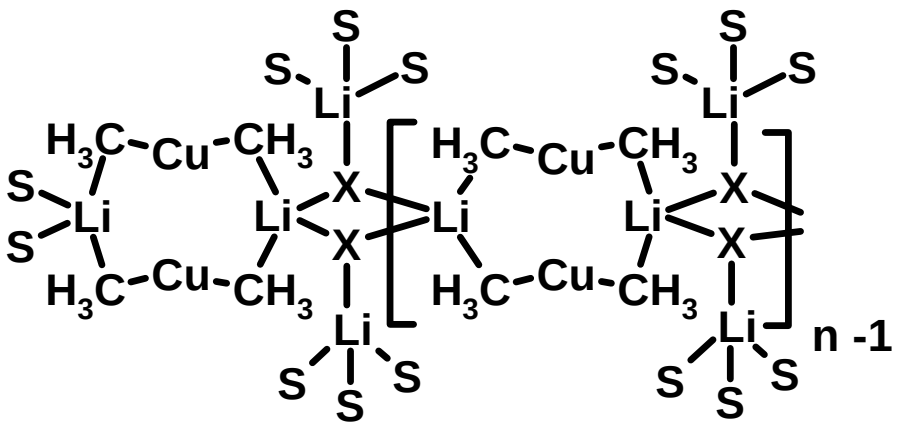

binuclear $Cu_A$ site in Cyo A



bis(oxazolin)-CuOTf complex




$[BrCu(Quinap)]_2$

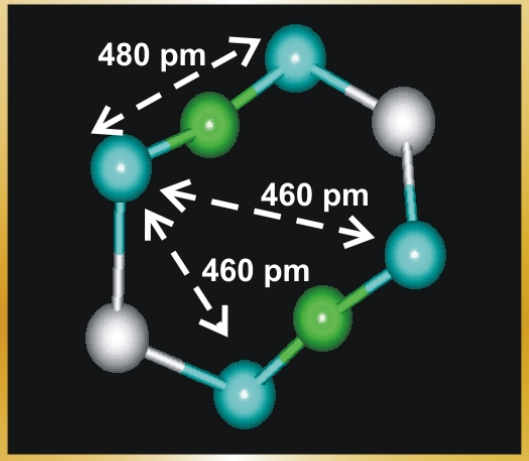



organocuprate

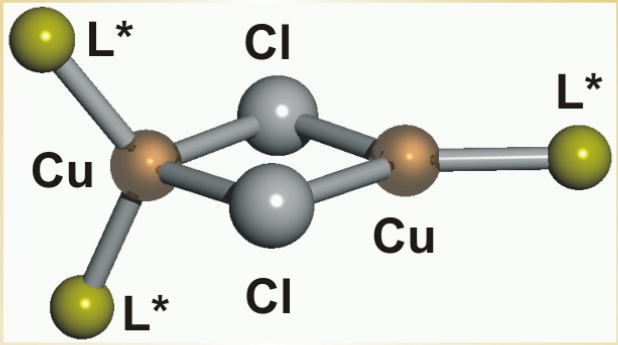
# Structure Elucidation of Copper Systems

R. M. Gschwind, *Chem. Rev.*, **2008,** *108*, 3029-53.

## Part 1: Organocuprate Reagents and Intermediates




## Part 2: Precatalytic Copper Complexes in Enantioselective 1.4 Additions to Enones



# Organocopper Compounds:
# Famous Reagents Effecting Carbon-Carbon Bonds

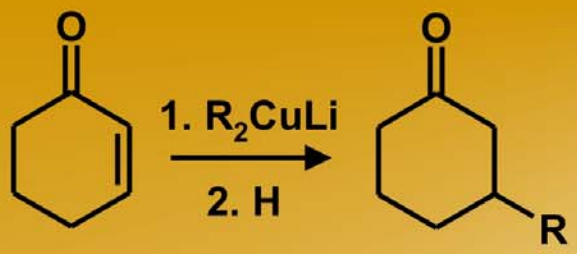
**chemo-, regio- and stereoselective**

**addition reactions**

**substitution reactions**

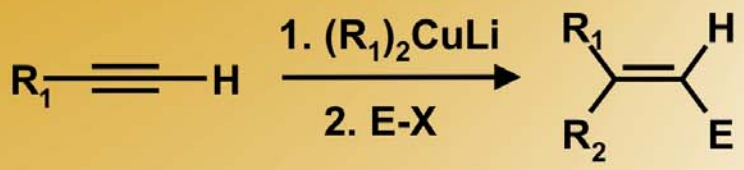
$R_2CuLi$
$RR'CuLi$
$RCu \cdot BF_3$
$R_5Cu_3Li_2$

**michael additions:**

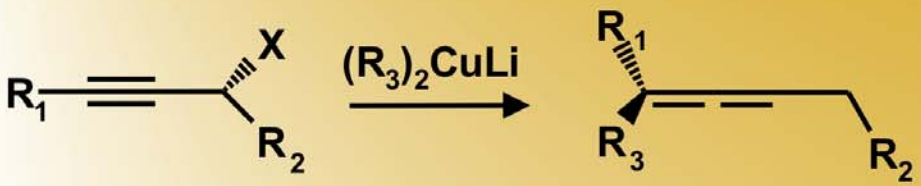



**allylic systems:**


**carbocupration:**




**propargylic systems:**

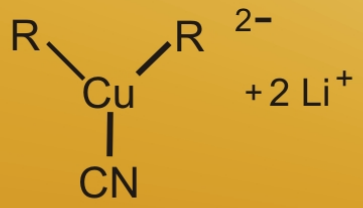



N. Krause (Ed.), *Modern Organocopper Chemistry,* Wiley-VCH, Weinheim, **2002**.

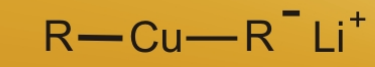
# Organocopper Reagents: Structure-Reactivity Correlations

**monomeric structure**

**influence of salt?**




"higher order"

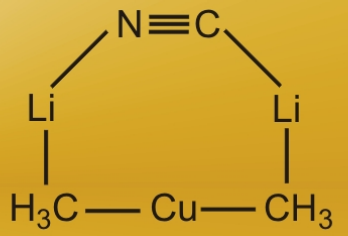



+ LiX X=CL, Br, I

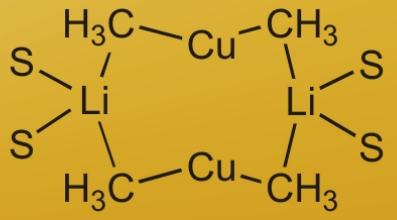
"lower order"

**$R_2CuLi$**

**$R_2CuLi \cdot LiX$**

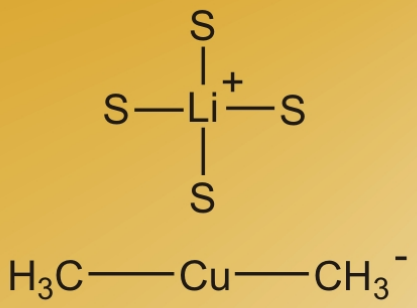



hetero-dimer

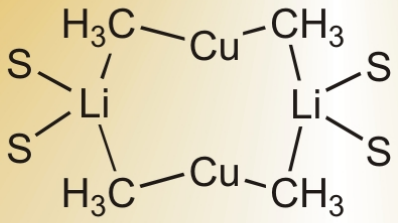



homo-dimer

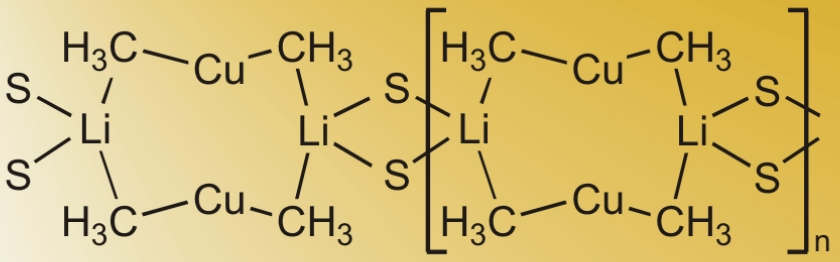
**aggregation?**




monomer




dimer

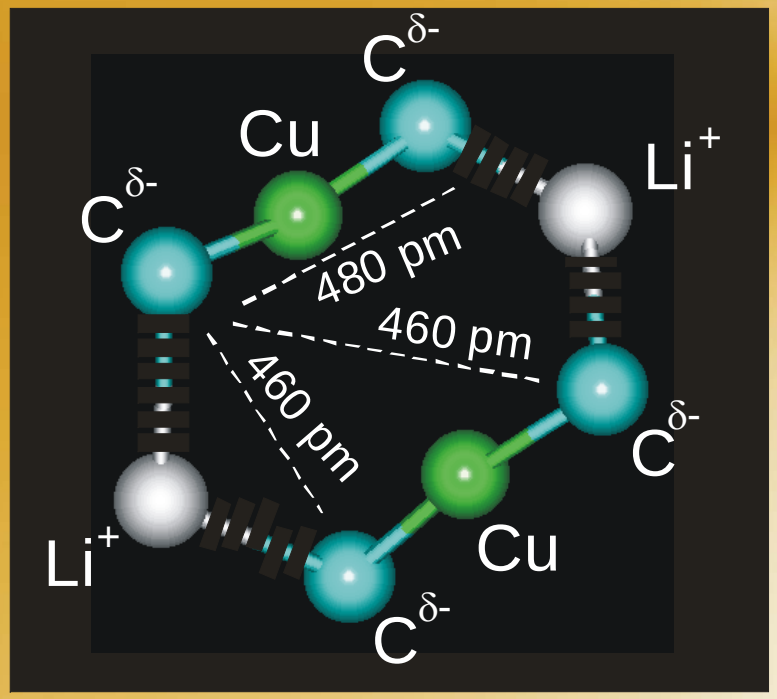



polymer

S = solvent molecule

# Challenges in Structure Determination of Organocuprates

aggregates of ion pairs → high symmetry → no scalar couplings detectable → dipolar interactions

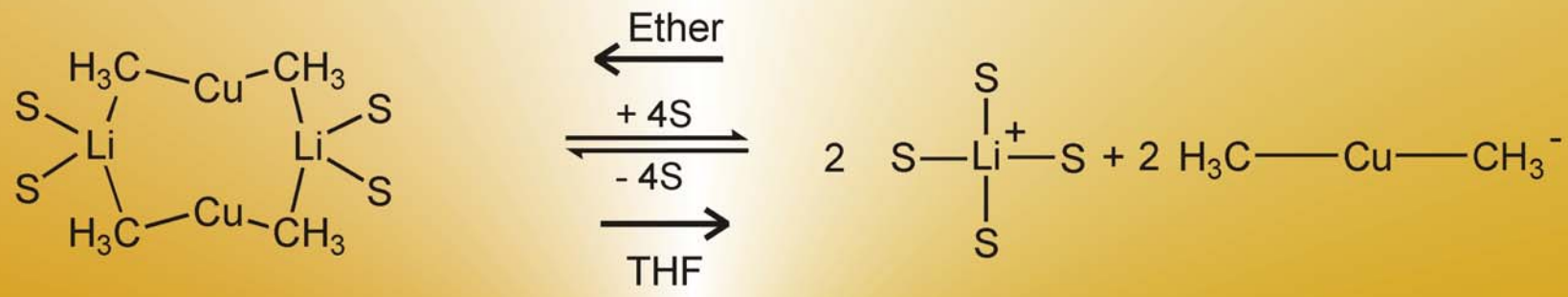



dipolar interactions → long range interactions

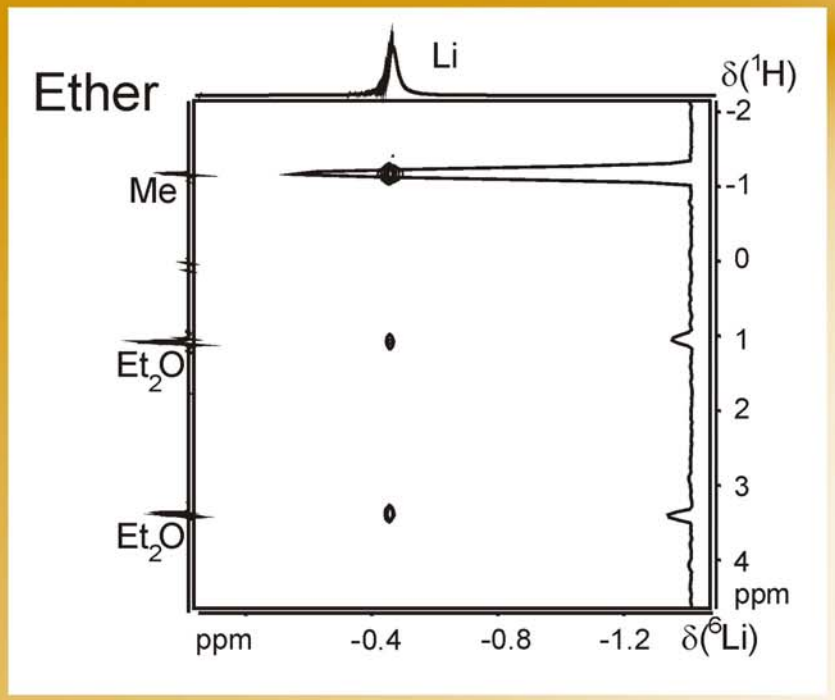
dipolar interactions → quadrupolar relaxation

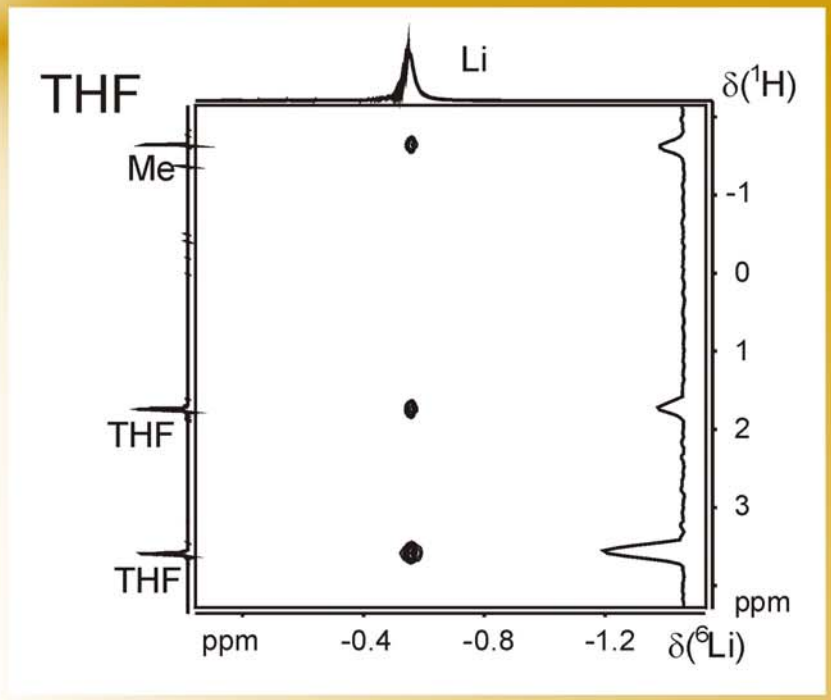
dipolar interactions → internal rotation

# Ion Pair Equilibria of Lithium Organocuprates in Solution



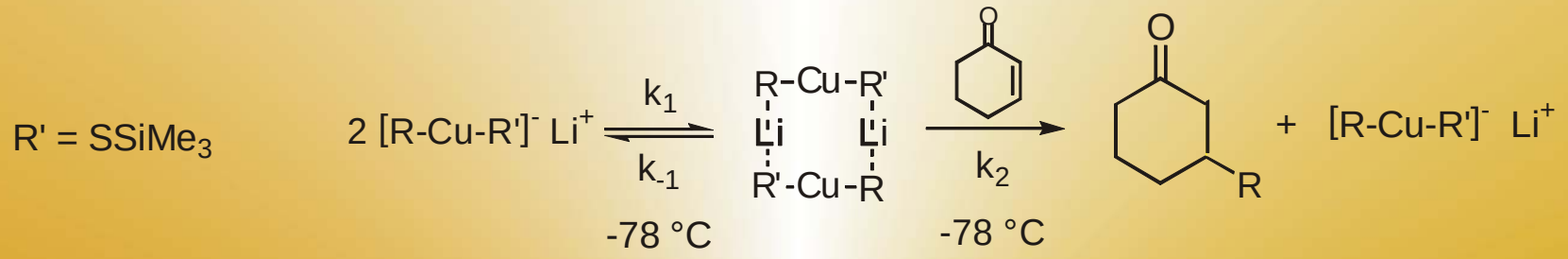

$^{1}H$, $^{6}Li$ HOESY spectra of $Me_2CuLi$ in:

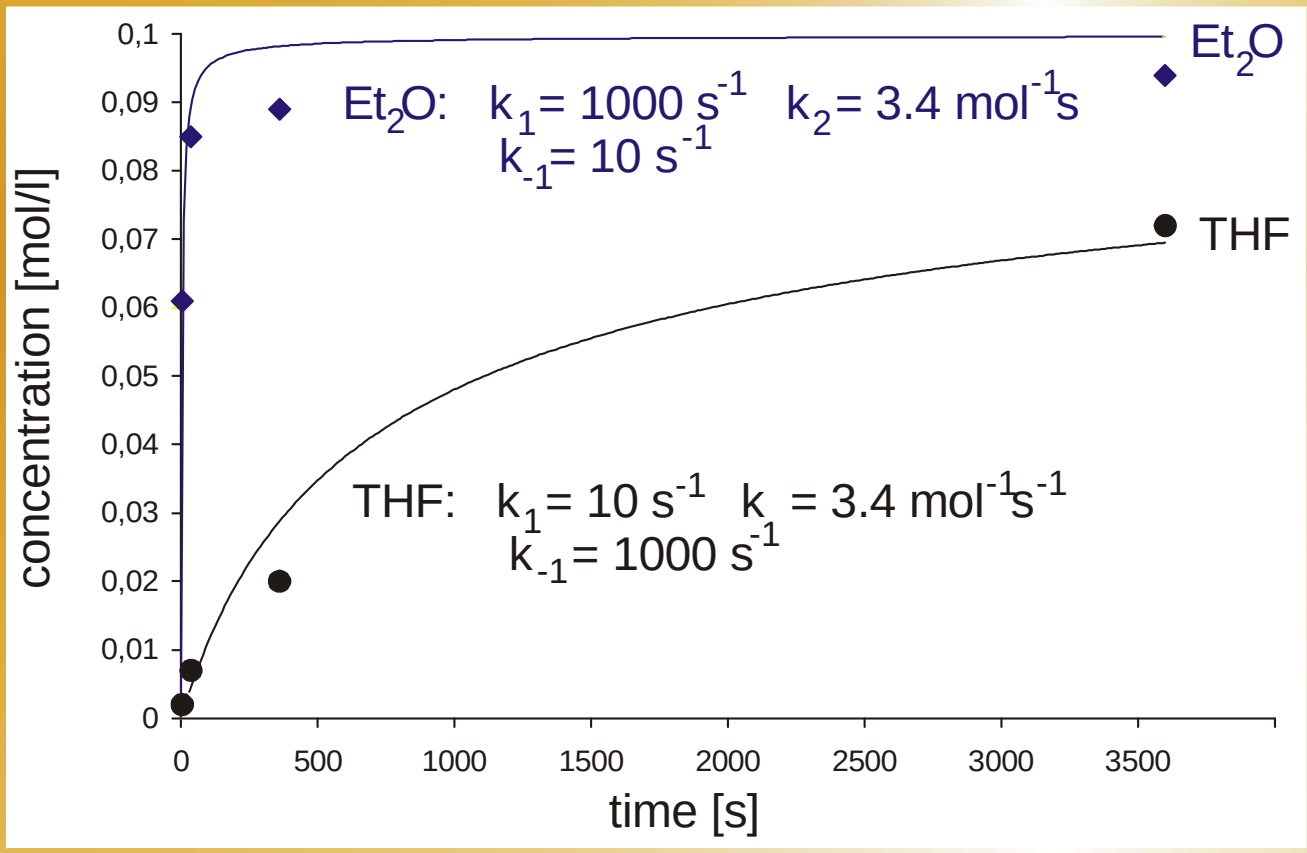


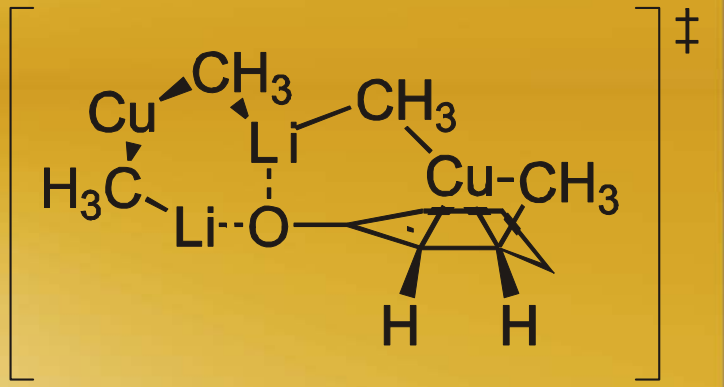




R. M. Gschwind *et al., Organometallics* **2000**, *19*, 2868-2873.

# Dimer as Reactive Species



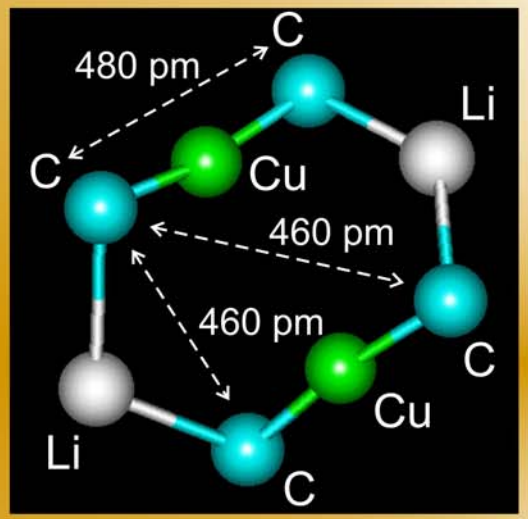
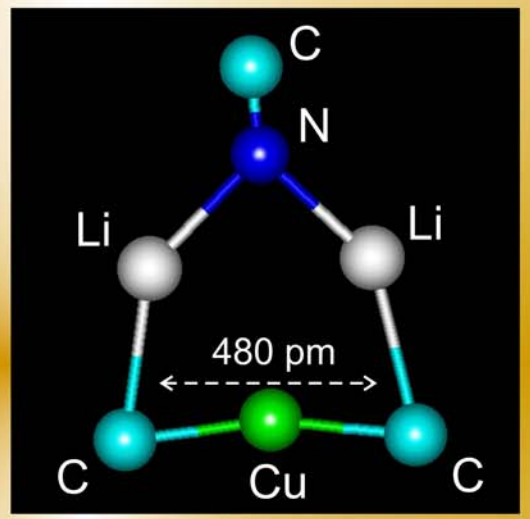
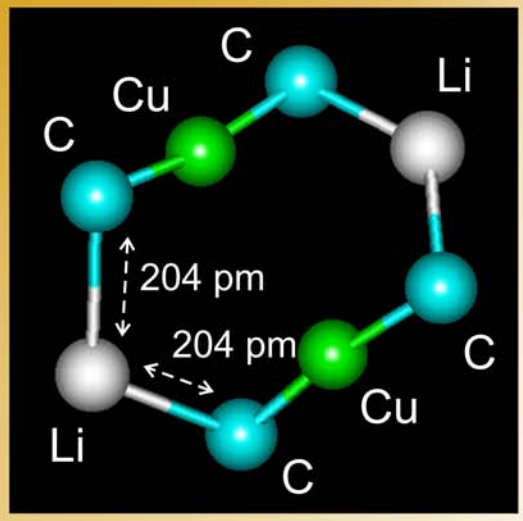
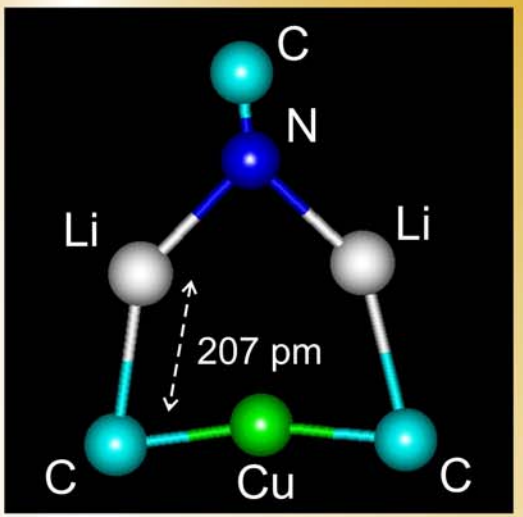




S. Mori and E. Nakamura
*Chem. Eur. J.* **1999**, *5*, 1534-1543.

M. John, G. Boche, R. M. Gschwind *et al., Chem. Eur. J.* **2000**, *6*, 3060-3068.

# Homodimer or Heterodimer?
# Distinction by Dipolar Couplings

| | homo-dimer | hetero-dimer | theoretical ratio homo-/hetero-dimer |
|---|---|---|---|
| $^{1}H,^{1}H$ NOE |  |  | **4.3 / 1** |
| $^{1}H,^{6}Li$ HOE |  |  | **2.2 / 1** |





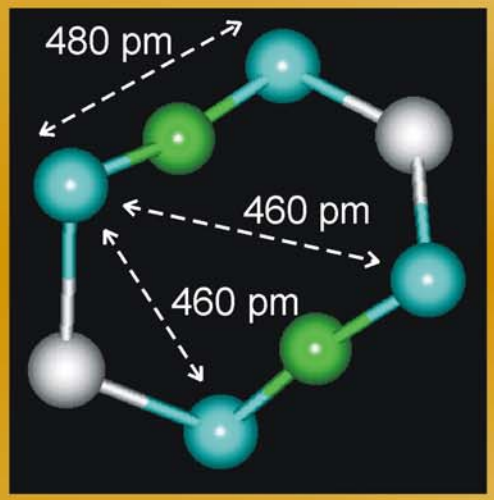


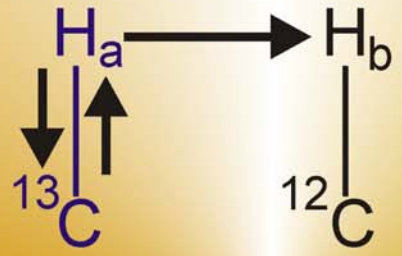


R. M. Gschwind *et al.*, *J. Am. Chem. Soc.* **2001**, *123*, 7299-7304.

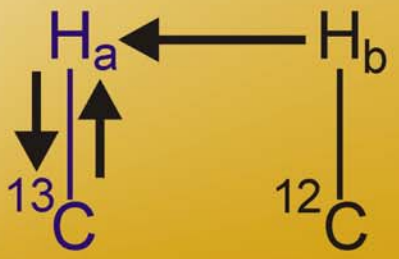
# NOESY-HSQC versus HSQC-NOESY:

**symmetry as challenge:**




GS-HSQC-NOESY




GS-NOESY-HSQC

Different Coherence Transfer Efficiencies

Symmetrical NOE cross peaks:

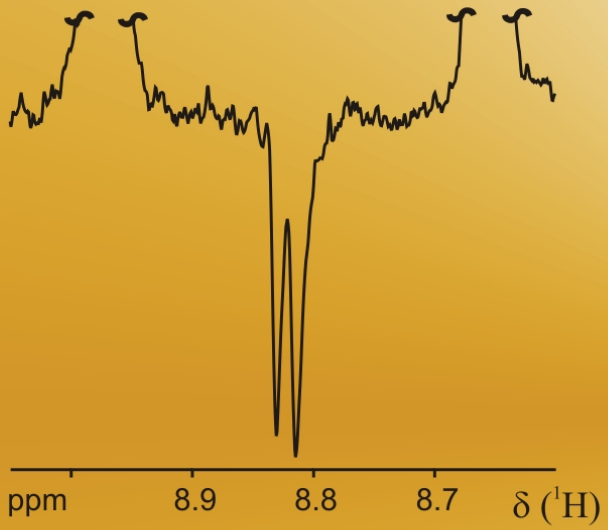
$$a_{AB}(\tau) = a_{BA}(\tau) = n_A n_B \sigma_{AB} M_0 K/(n_A+n_B)$$

Diffusion effects (Stejskal-Tanner)

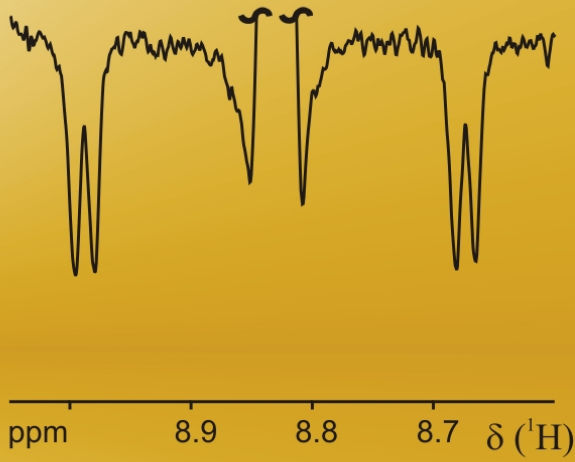
$$I/I_0 = \exp[-D\gamma^2 g^2 \delta^2 (\Delta - \delta/3)]$$

# Intensity Comparison

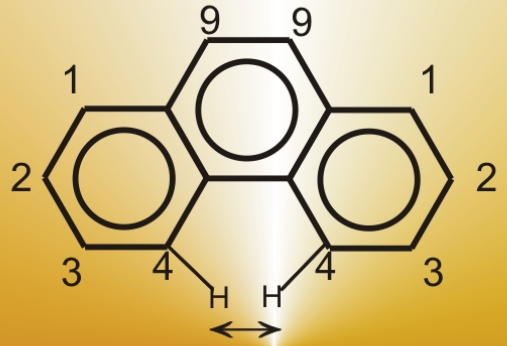
## GS-HSQC-NOESY

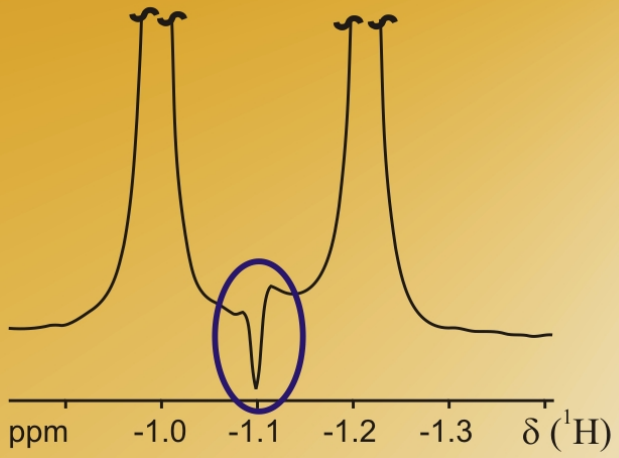



## GS-NOESY-HSQC

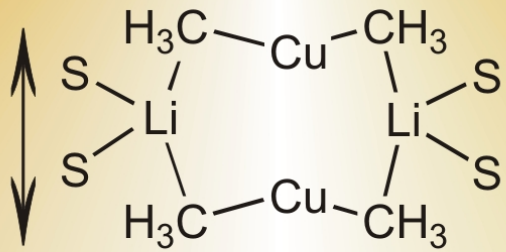


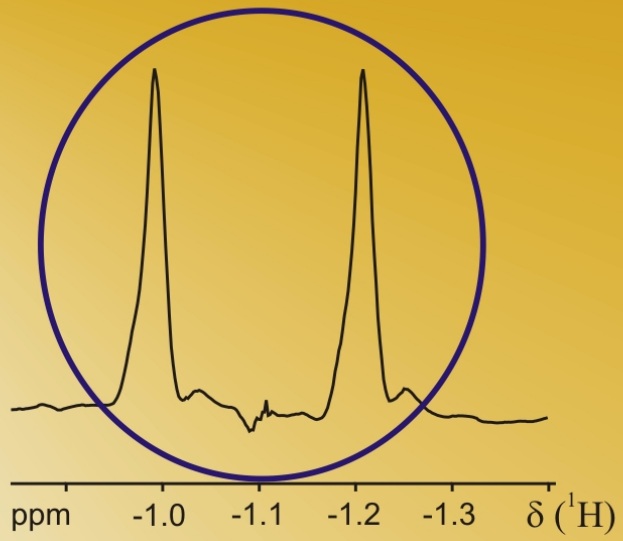

## Phenantrene




## Dimethylcuprate

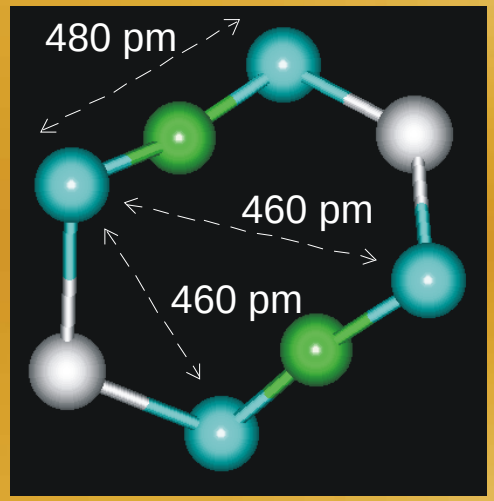


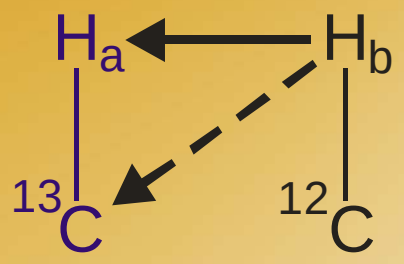




R. M. Gschwind, X. Xie, P. R. Rajamohanan, *Magn. Reson. Chem.* **2004**, *42*, 308-312.

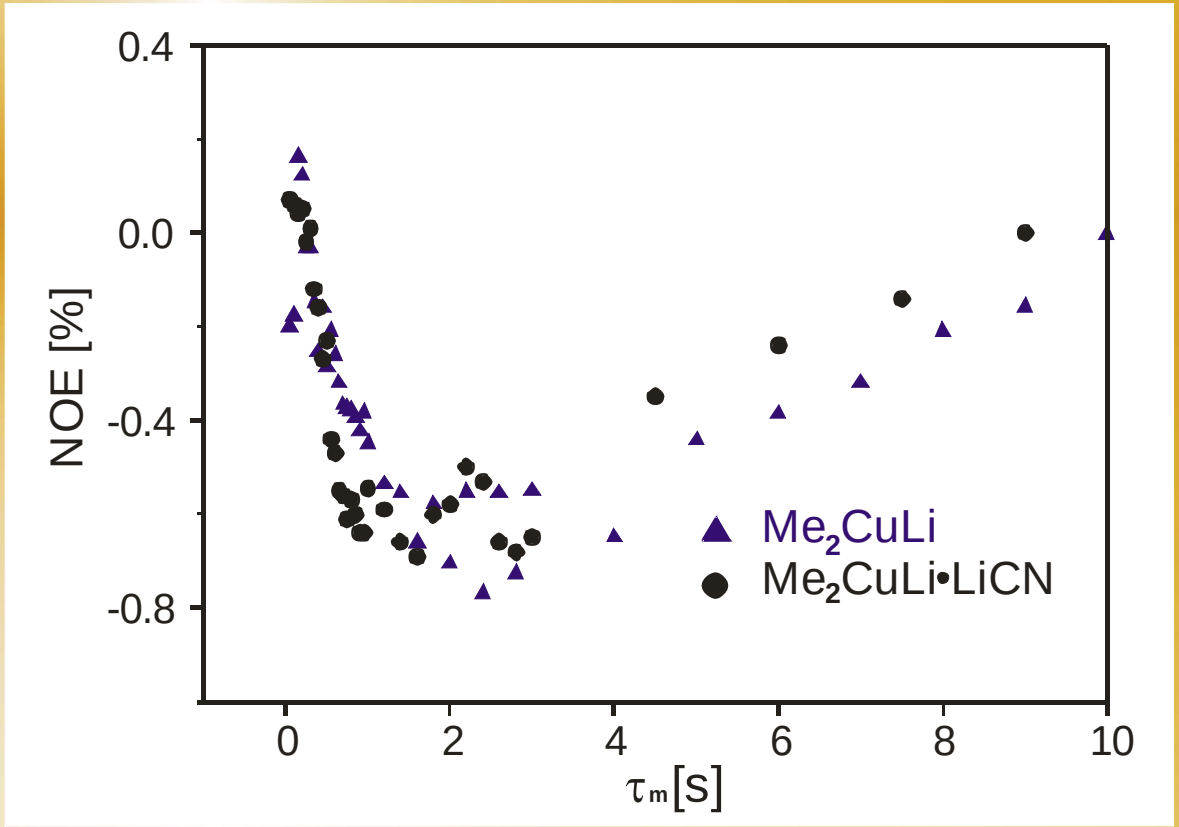
# $^1$H,$^1$H NOE:
# $Me_2CuLi{\cdot}LiCN$ in DEE is Homo-Dimeric

**symmetry as challenge:**



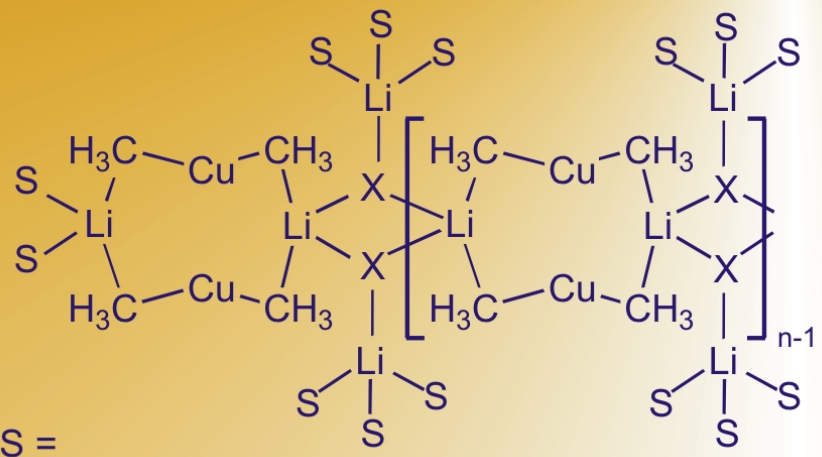

**selective $^1$H,$^1$H HSQC-NOESY buildup curves:**




R. M. Gschwind et al., *J. Am. Chem. Soc*. **2001**, *123,* 7299-7304.

# Diffusion Coefficients *D*, Stokes Radii $r_S$, and Aggregation Indices *n* of Organocuprates (0.38 M) in $Et_2O$ at 239 K

| Compound | *D* [$10^{-9}$ $m^2s^{-1}$] | $r_s$ [$10^{-10}$ m] | *n* |
|---|---|---|---|
| $[(Me_3SiCH_2)_2CuLi]_2(Et_2O)_2$ | 0.42 | 6.39 | **1.7** |
| $[(Me_3SiCH_2)_2CuLi]_2(LiI)_2(Et_2O)_6$ | 0.34 | 6.82 | **1.3** |
| $[(Me_3SiCH_2)_2CuLi]_2(LiCN)_2(Et_2O)_6$ | 0.18 | 9.17 | **3.2** |
| $[Me_2CuLi]_2(Et_2O)_2$ | 0.29 | 6.17 | **3.1** |
| $[Me_2CuLi]_2(LiI)_2(Et_2O)_6$ | 0.28 | 6.83 | **1.9** |
| $[Me_2CuLi]_2(LiCN)_2(Et_2O)_6$ | 0.20 | 8.88 | **4.5** |

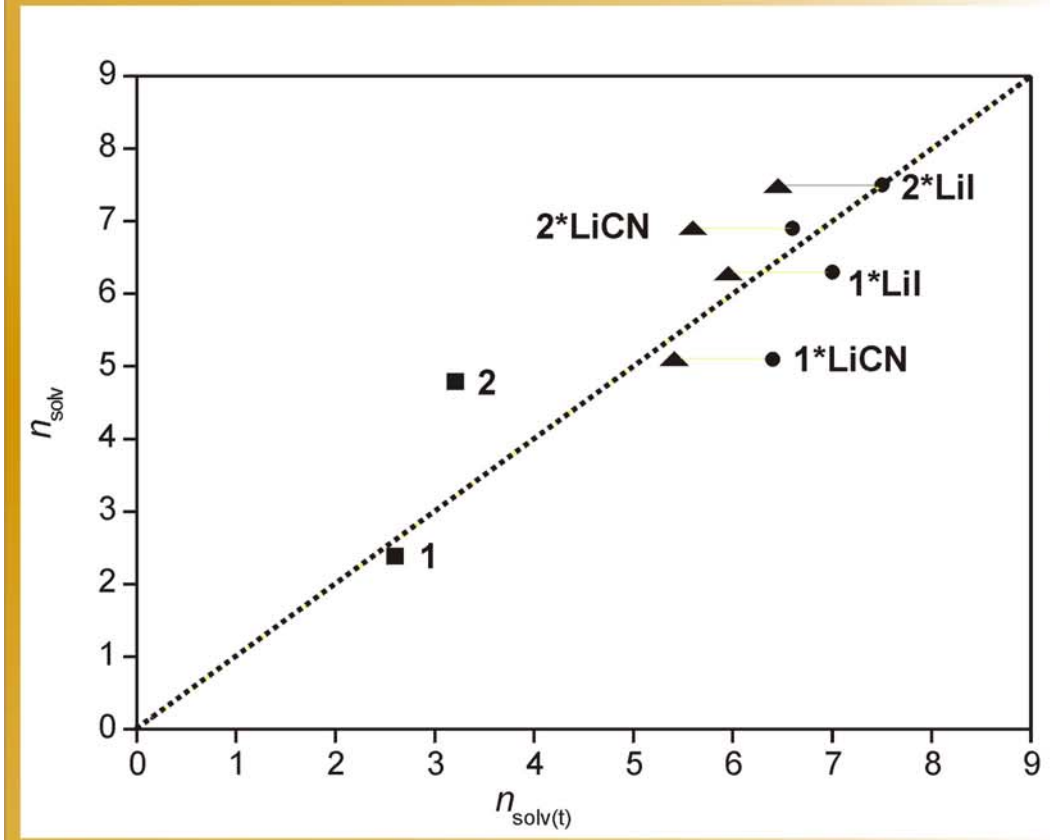



S = solvent molecule

- $E_{rel}$: $LiCNLi^+ < LiBrLi^+ < LiILi^+$

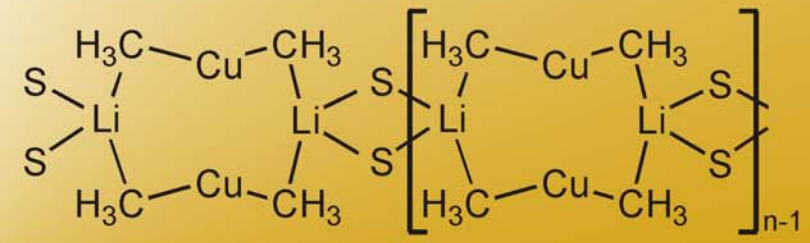
X.Xie, C. Auel, W. Henze, R. M. Gschwind, J. Am. Chem. Soc. 2003, 125, 1595-1601.

# Solvent Analysis: Confirmation of Models




**1** $Me_2CuLi$ **2** $(Me_3SiCH_2)_2CuLi$

■



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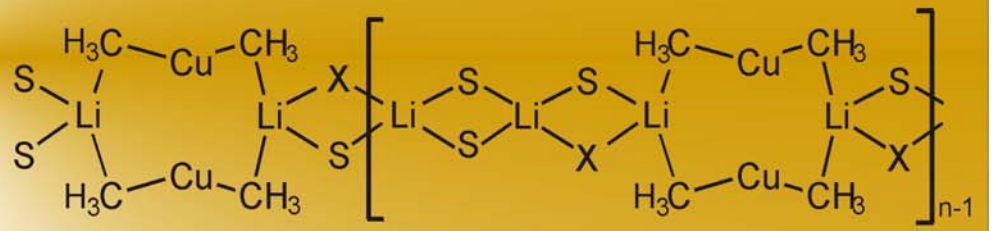
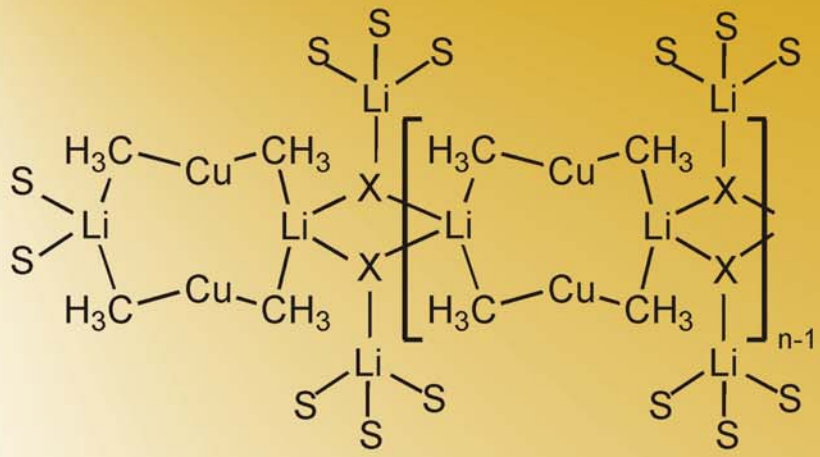


●



S = solvent molecule

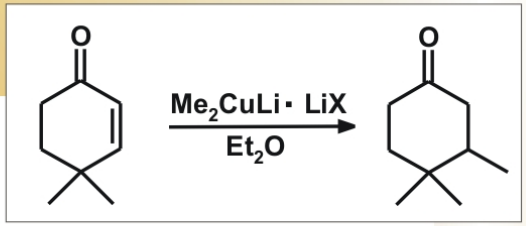
# Reactivity Comparison of Iodo- and Cyanocuprates in $Et_2O$

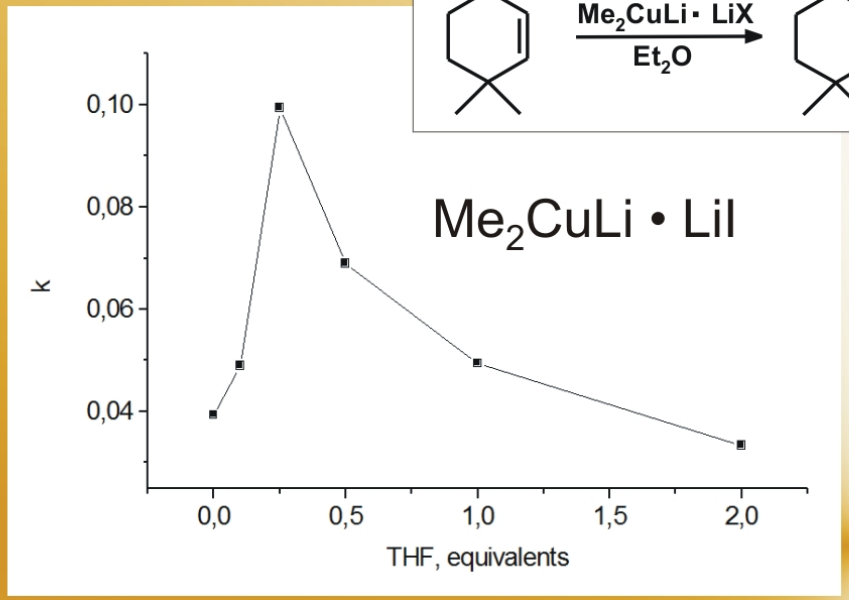
LRP data for the addition reaction of organocuprates with 2-cyclohexenone

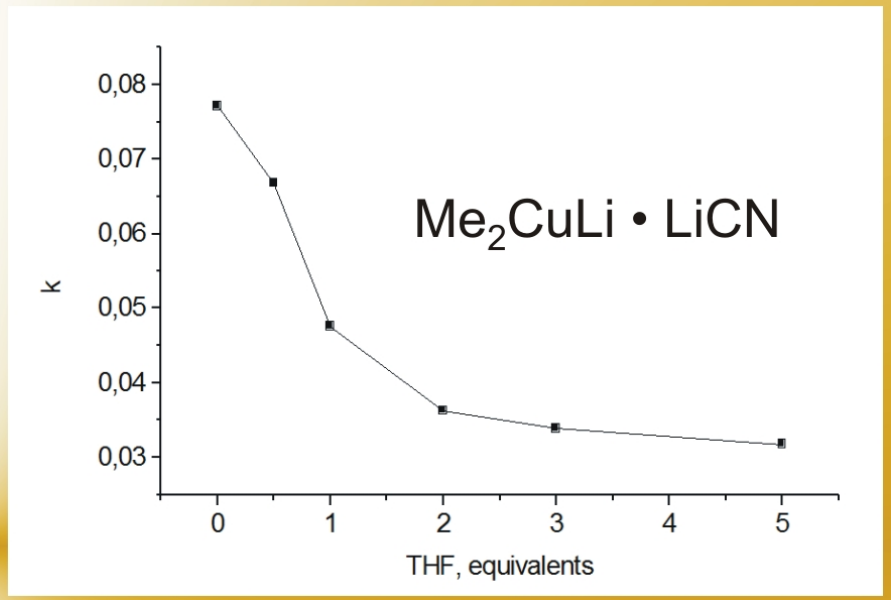
| Compound | Time [h] | Yield [%] |
|---|---|---|
| $Me_2CuLi{\cdot}LiI$ | 1 | 80 |
| | 0.1 | 52 |
| | 0.01 | 47 |
| | 0.001 | 32 |
| $Me_2CuLi{\cdot}LiI{\cdot}2THF$ | 1 | 81 |
| | 0.1 | 83 |
| | 0.01 | 69 |
| | 0.001 | 47 |
| $Me_2CuLi{\cdot}LiCN$ | 1 | 37 |
| | 0.1 | 27 |
| | 0.01 | 21 |
| | 0.001 | 5.3 |

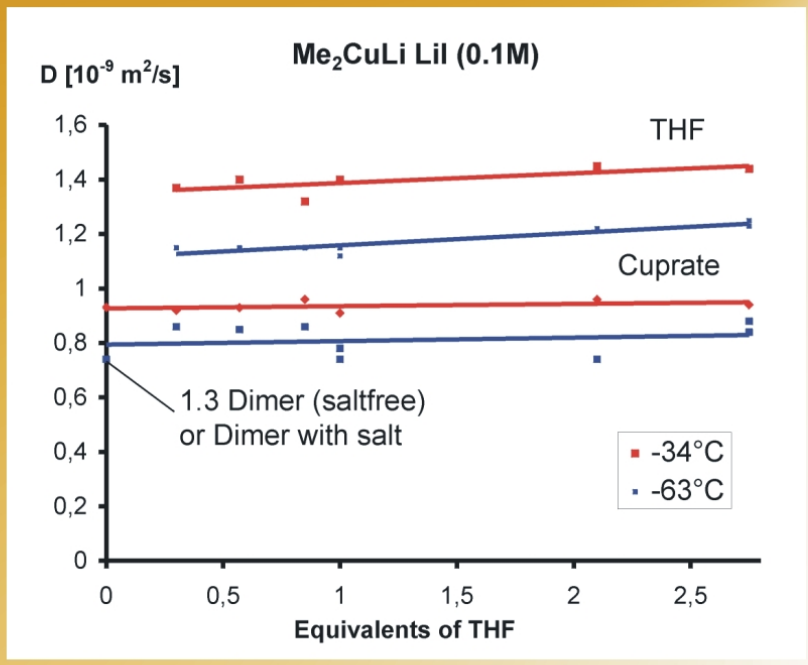

S. H. Bertz *et al., Chem. Eur. J.,* **1999**, *5*, 2680-2691.

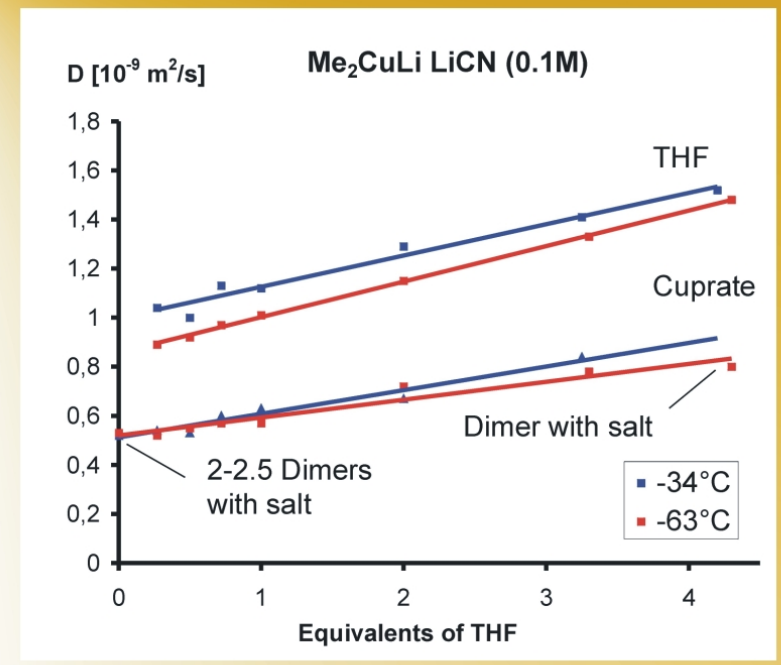
# Reaction Acceleration and Disaggregation by THF?



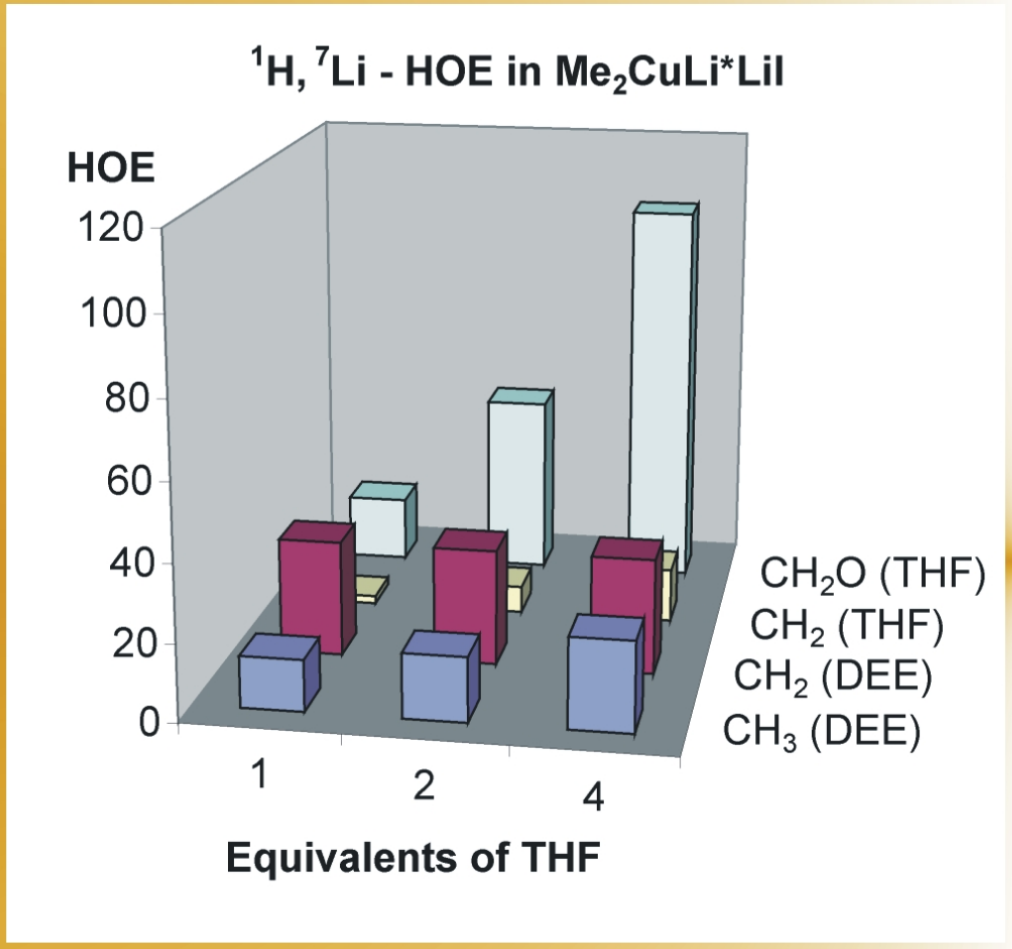



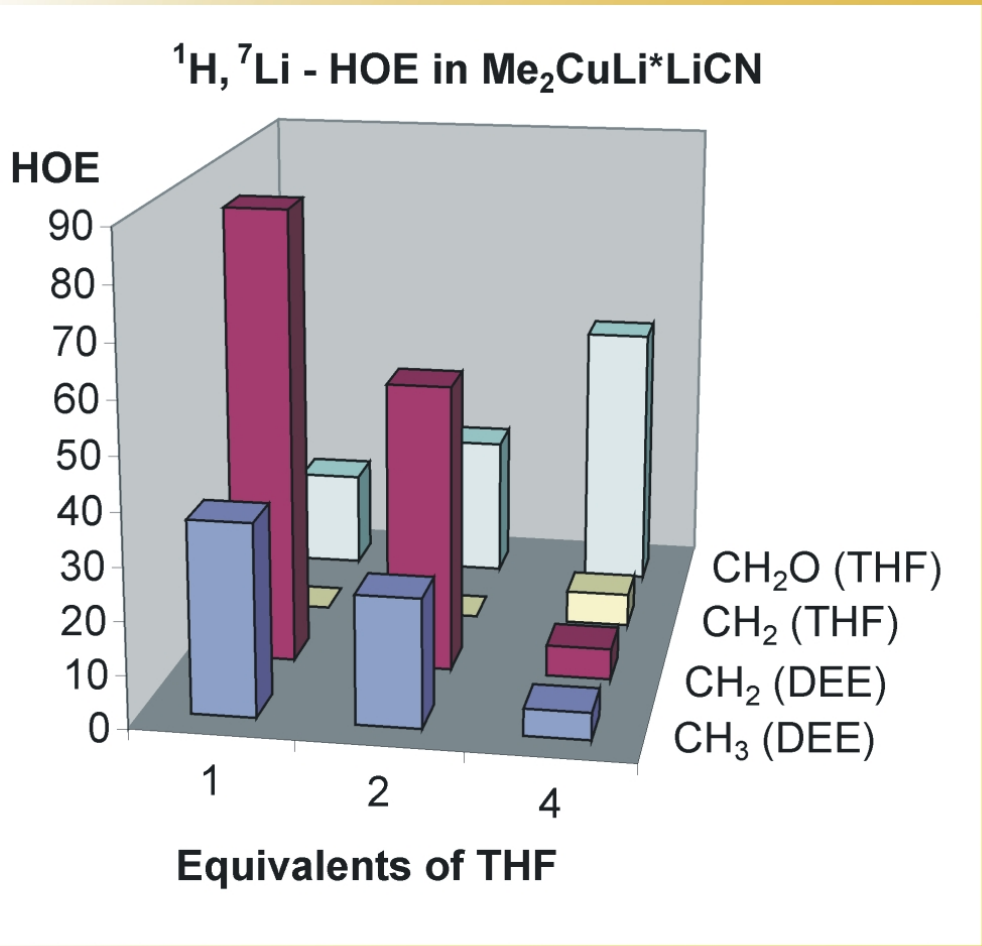



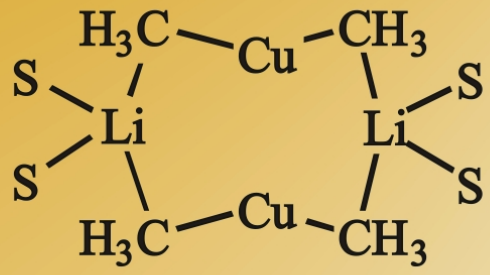




W. Henze, A. Vyater, N. Krause, R. M. Gschwind, *J. Am. Chem. Soc.*, **2005**, *127*, 17335-42.

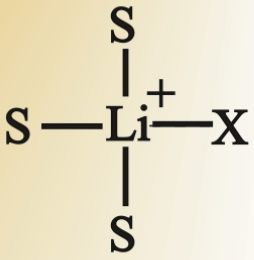
# Addition of THF:
# Increase of Coordination versus Replacement

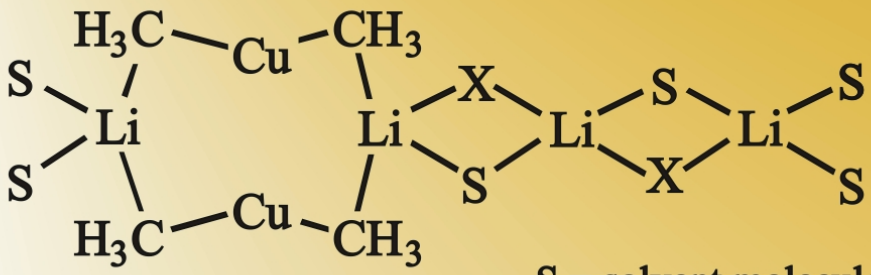


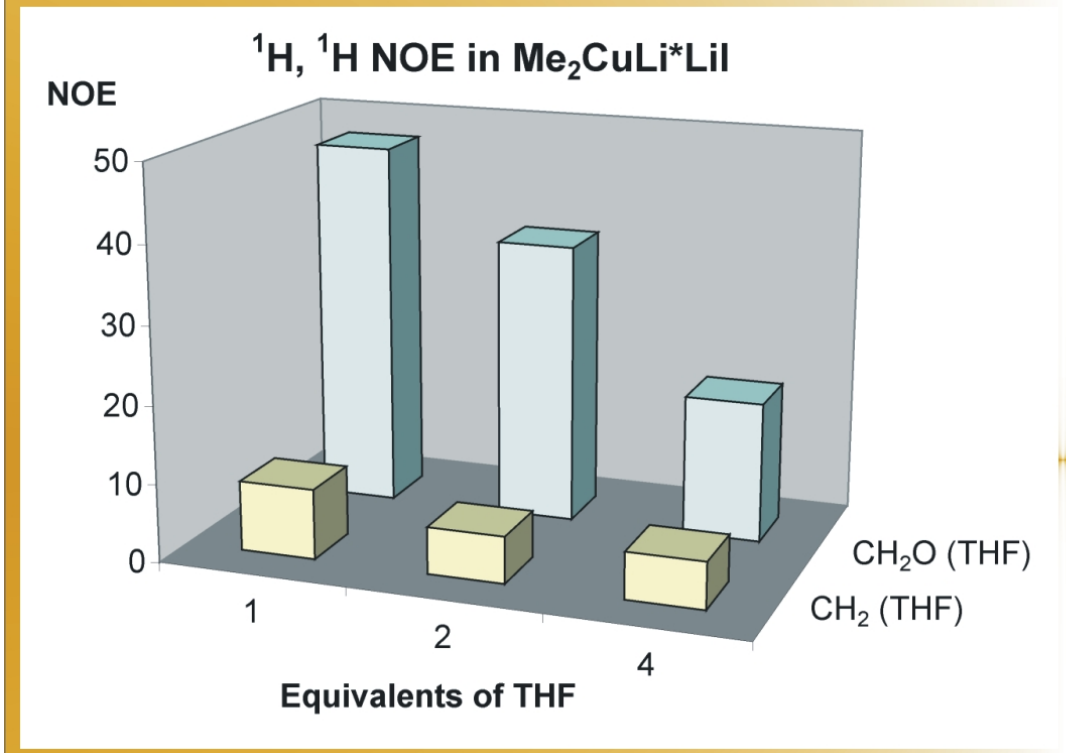

2

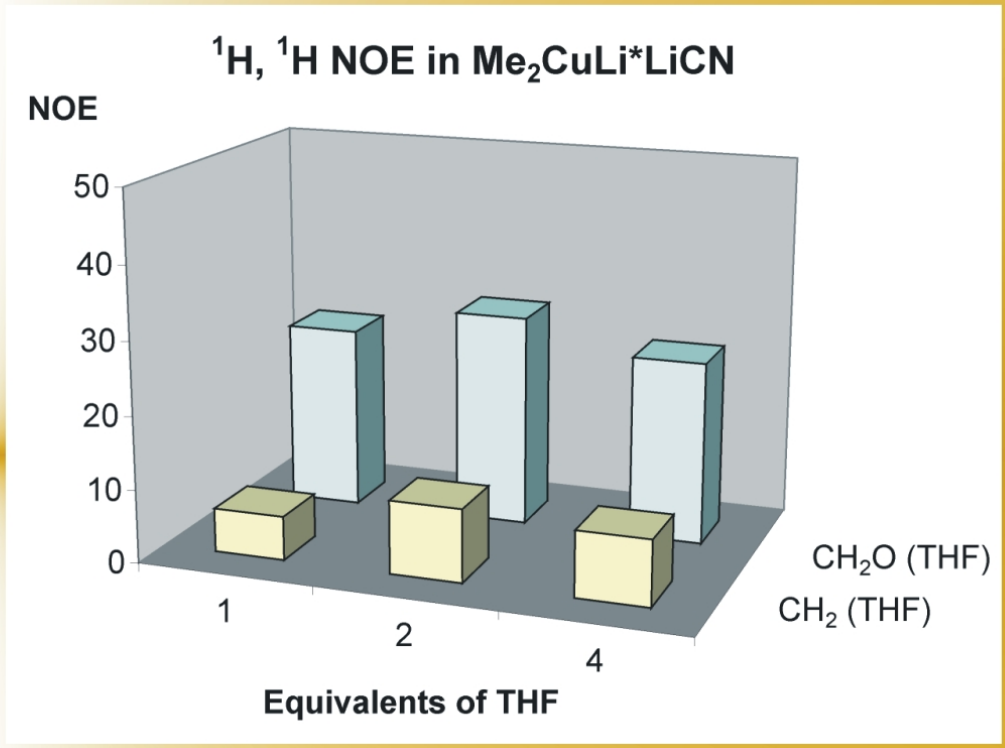


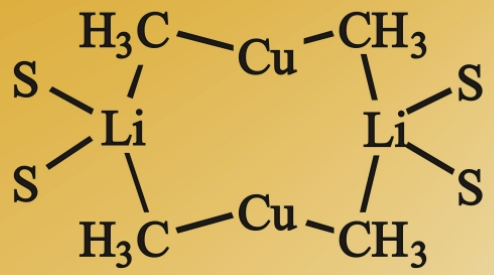




S = solvent molecule

# Addition of THF:
# Separation of Salt as well as Structural Stability

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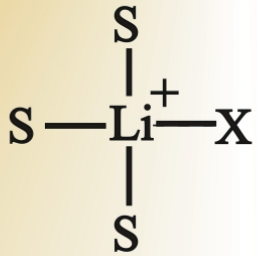
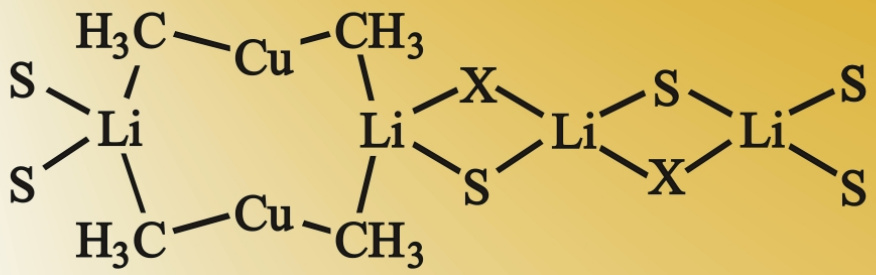
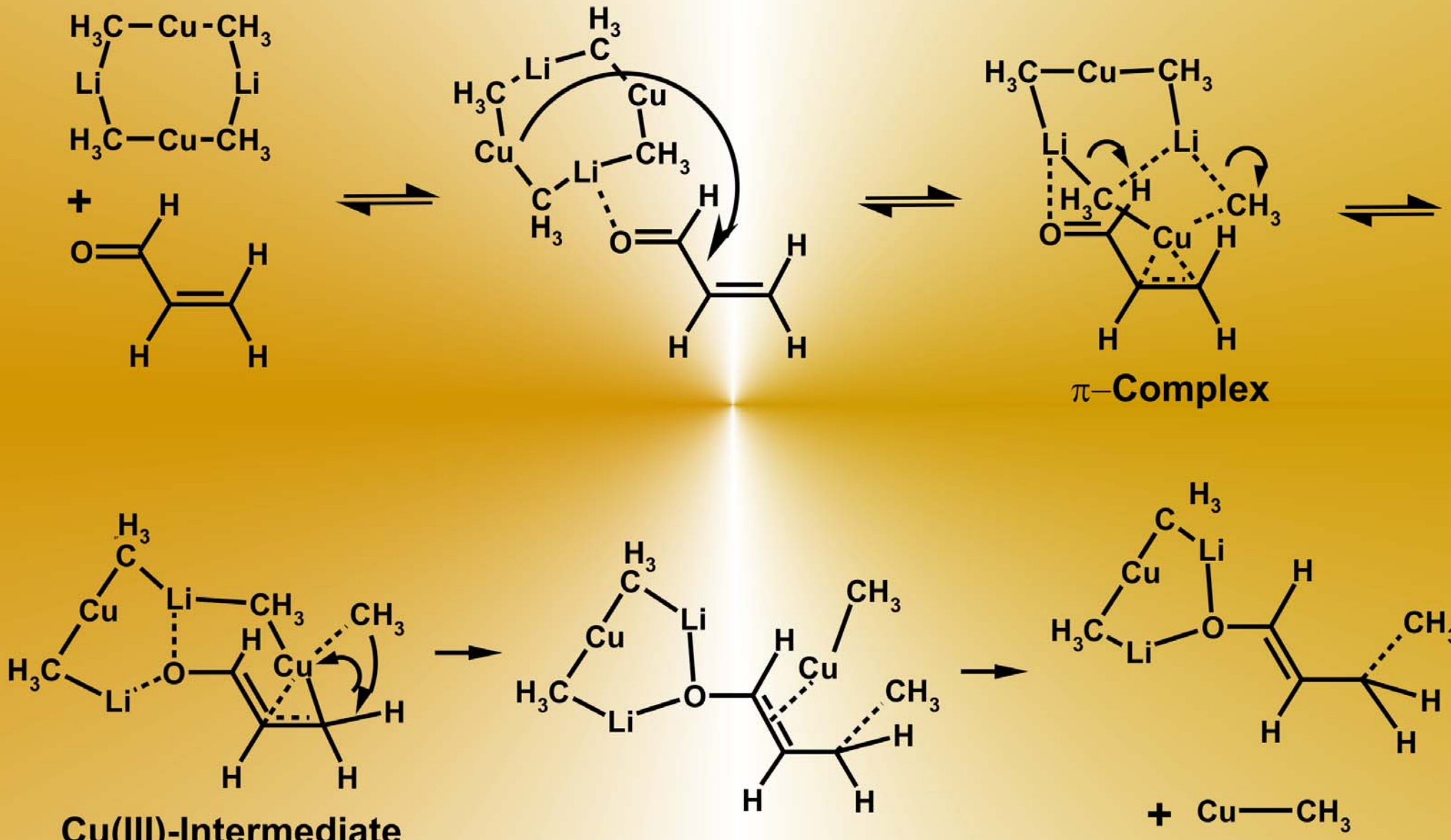


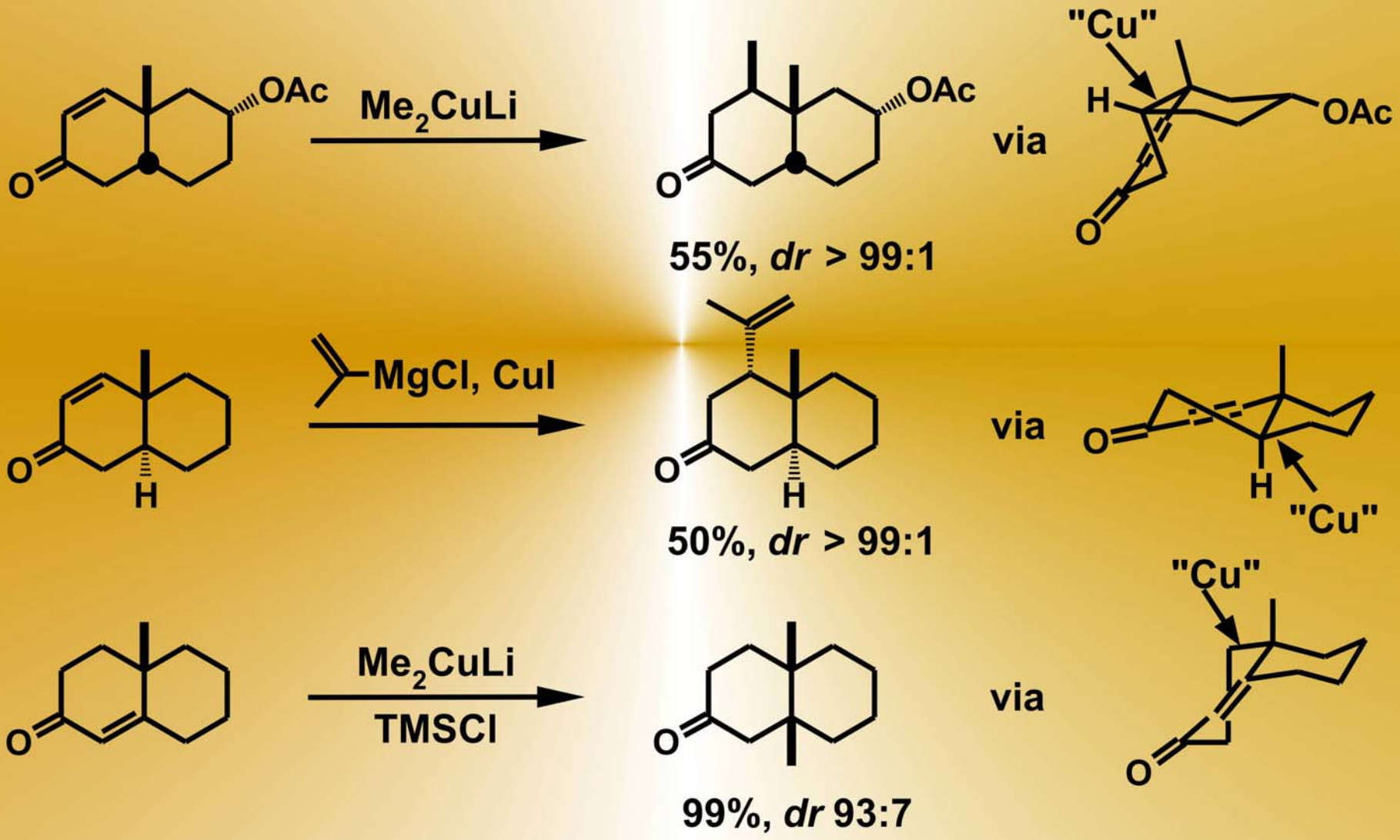

S = solvent molecule

# π–Complexes and Cu(III)-Intermediates in Conj. Additions



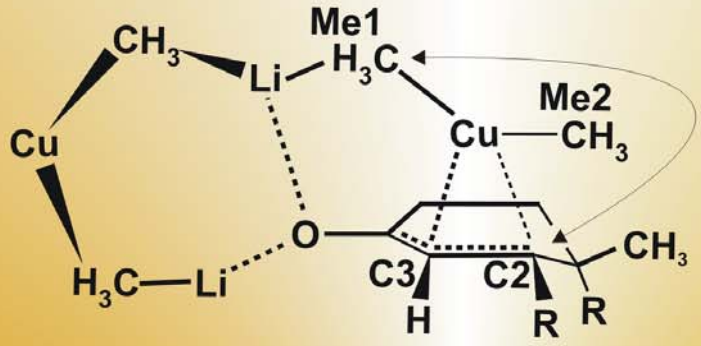

E. Nakamura, S. Mori, K. Morokuma *J. Am. Chem. Soc.*, **2000**, *122*, 7294-307.

# Diastereoselectivities in Conjugate Additions to Chiral Bicyclic Cyclohexenones



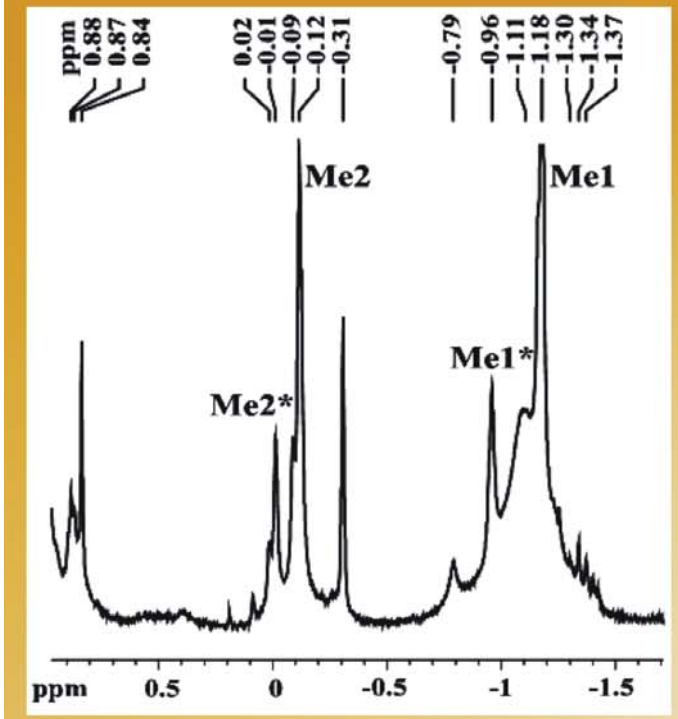

B. Breit, P. Demel, in *Modern Organocopper Chemistry,* (N. Krause, Ed.) Wiley-VCH: Weinheim, 2002.

# Identification of 2 π - Complex Conformations

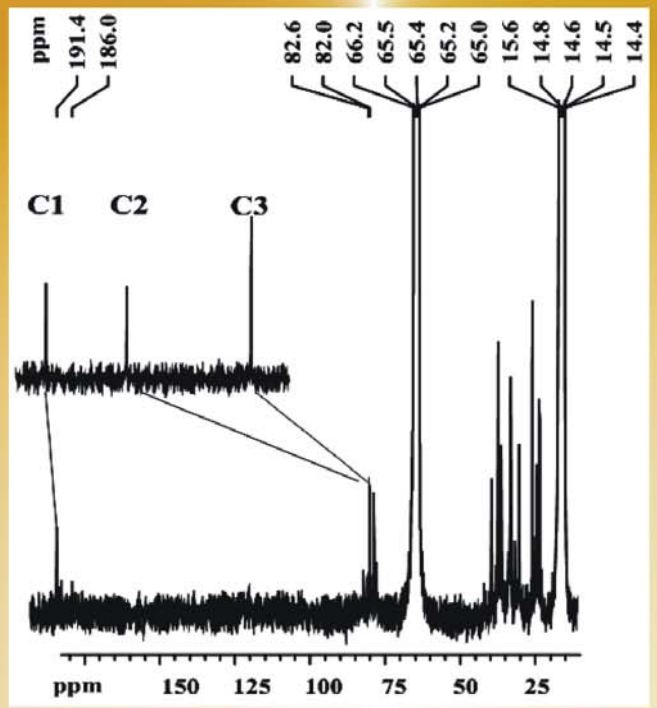



$Me_2CuLi$ • LiI + **1** in diethyl ether at 170 K

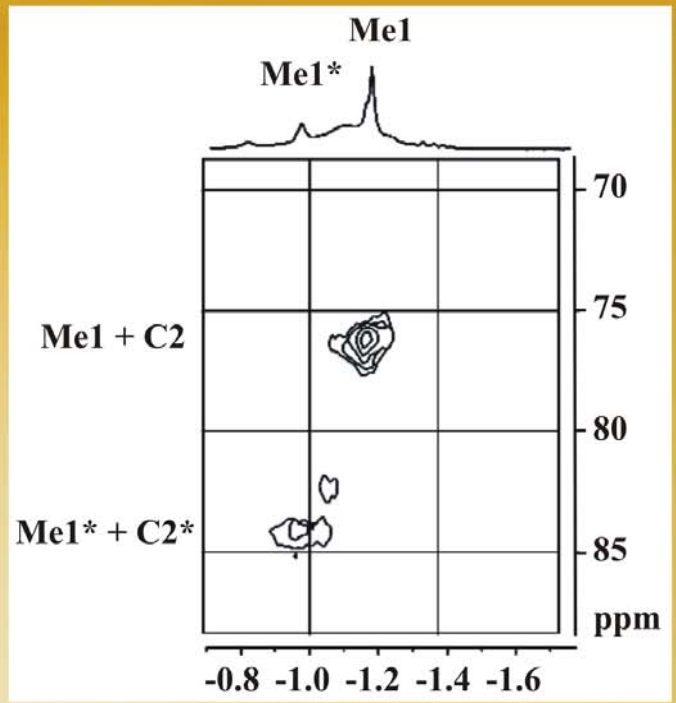
$^1$H NMR




$^{13}$C NMR



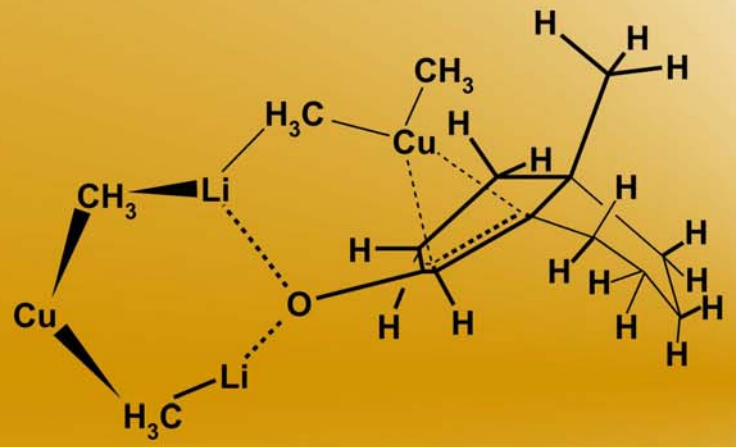

$^1$H, $^{13}$C INEPT INADEQUATE



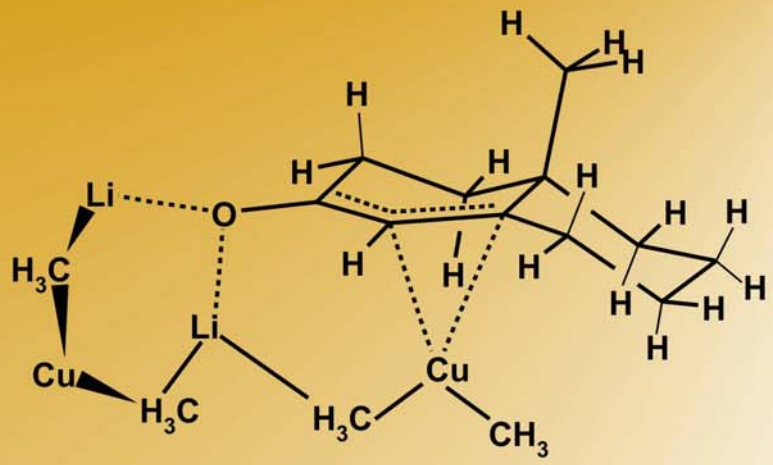

W. Henze, T. Gärtner, R. M. Gschwind, *J. Am. Chem. Soc.*, **2008**, *130,* 13718-13726.

# α - and β Face π Intermediates

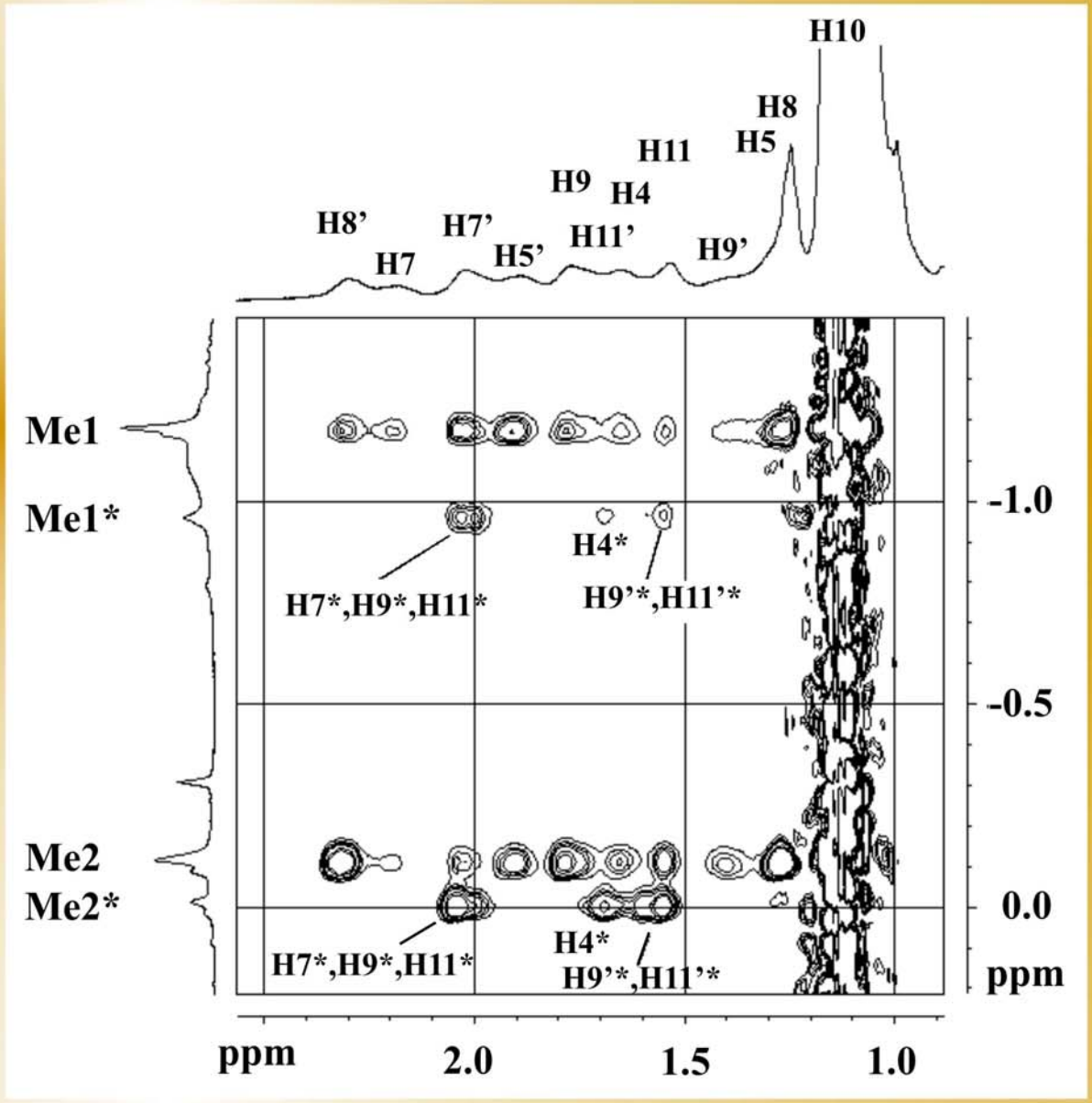
major conformation




minor conformation

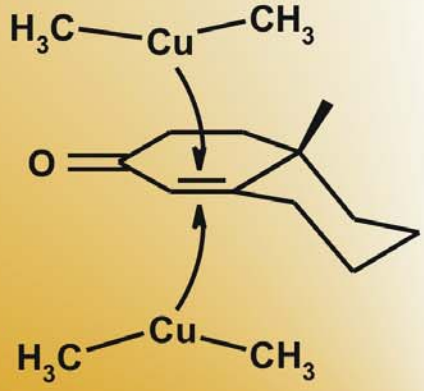



$^{1}$H,$^{1}$H NOESY in Diethylether at 180 K

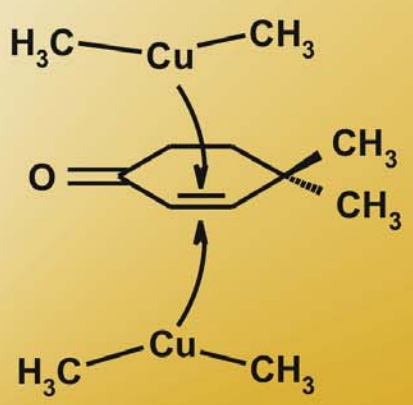


# Simplification of Spectra by Achiral Enones

a)

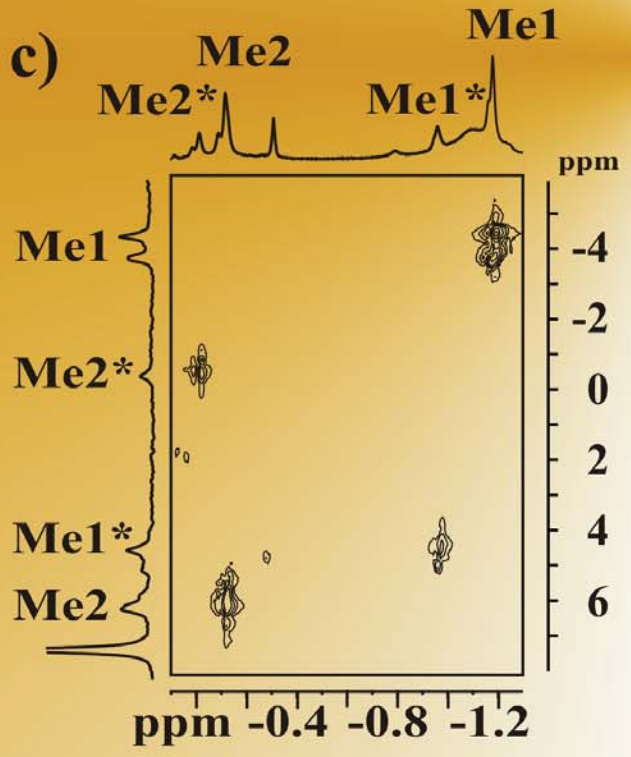



b)

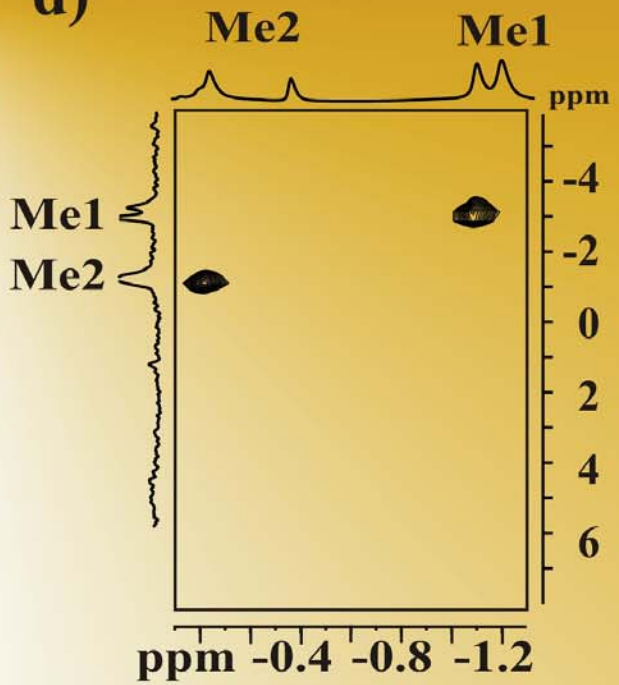



$^{1}H, ^{13}C$ HMQC Spectra in diethyl ether at 180 K

c)

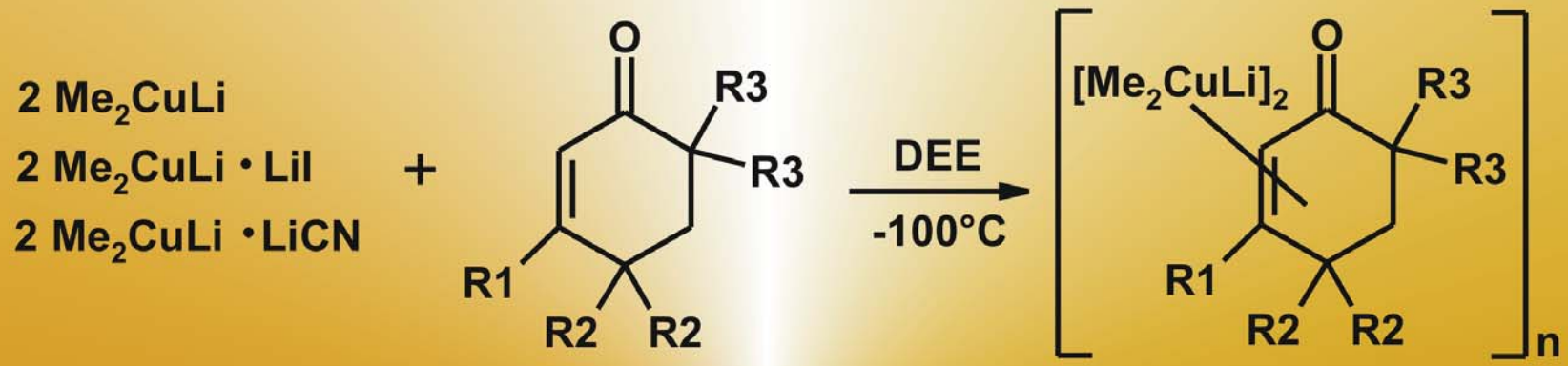



d)

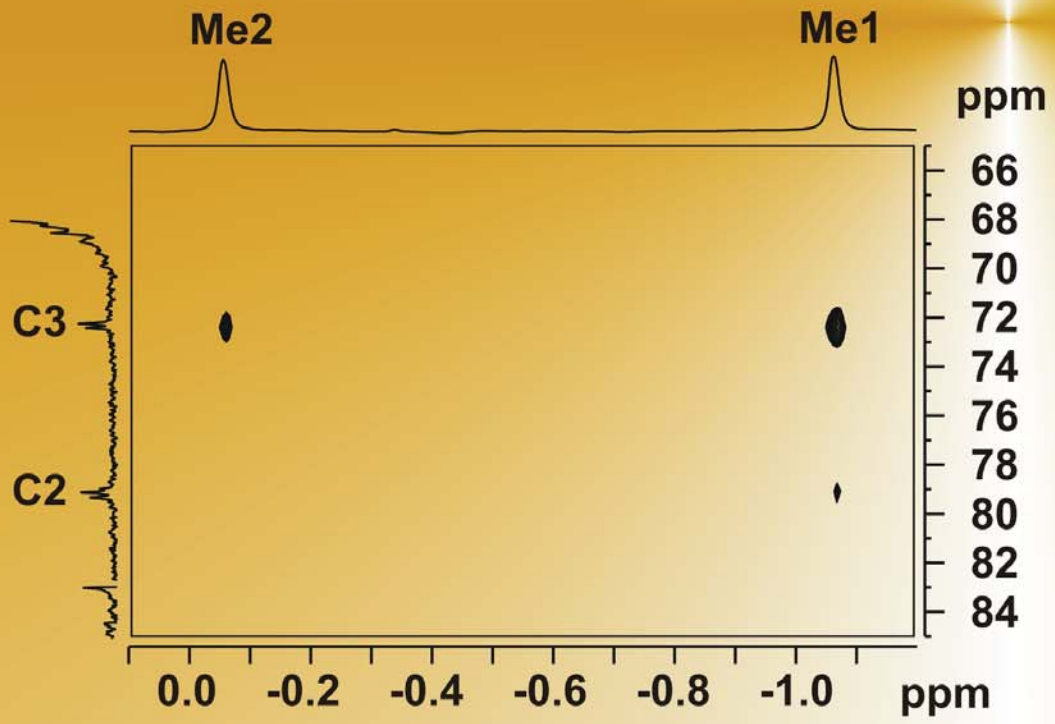


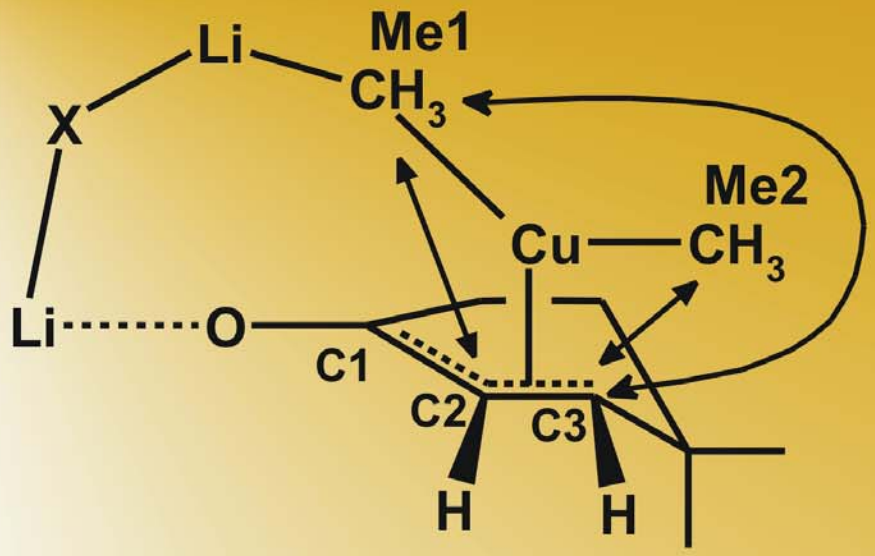

W. Henze, T. Gärtner, R. M. Gschwind, *J. Am. Chem. Soc.*, **2008**, *130,* 13718-13726.

# π–Complex Intermediates in Conjugate Addition Reactions




$^{1}H,^{13}C$-HMBC in $Et_2O$ at 170 K

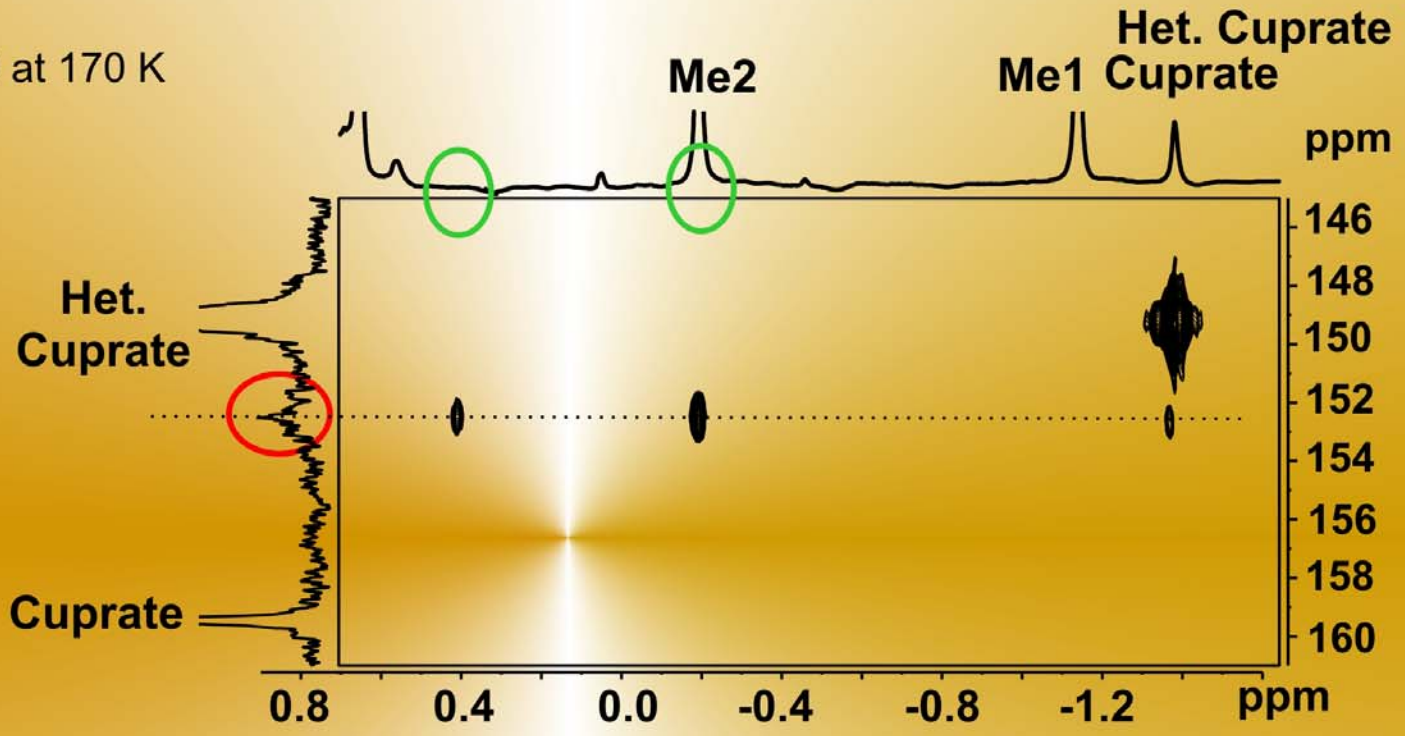


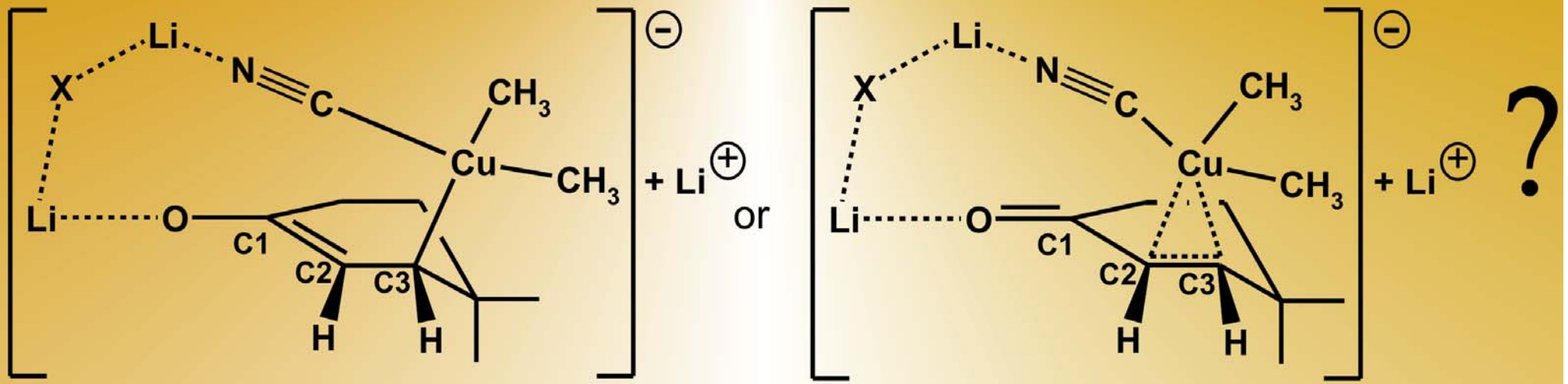




W. Henze, T. Gärtner, R. M. Gschwind, *J. Am. Chem. Soc.*, **2008**, *130,* 13718-13726.

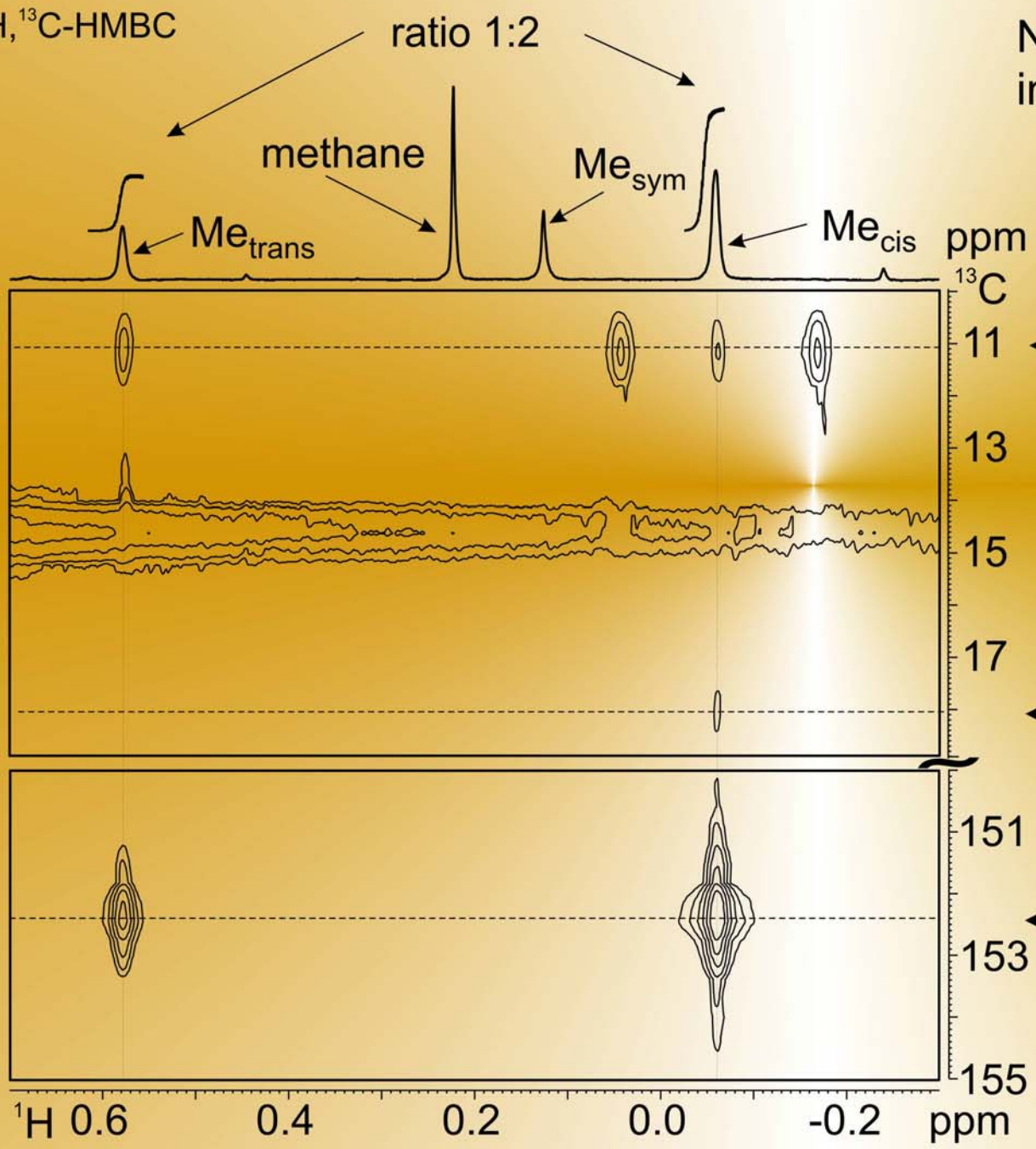
# Detection of Scalar Couplings to Cyanide in a Minor Intermediate Species using $Cu^{13}CN$

$^{1}H,^{13}C$-HMBC in $Et_2O$ at 170 K

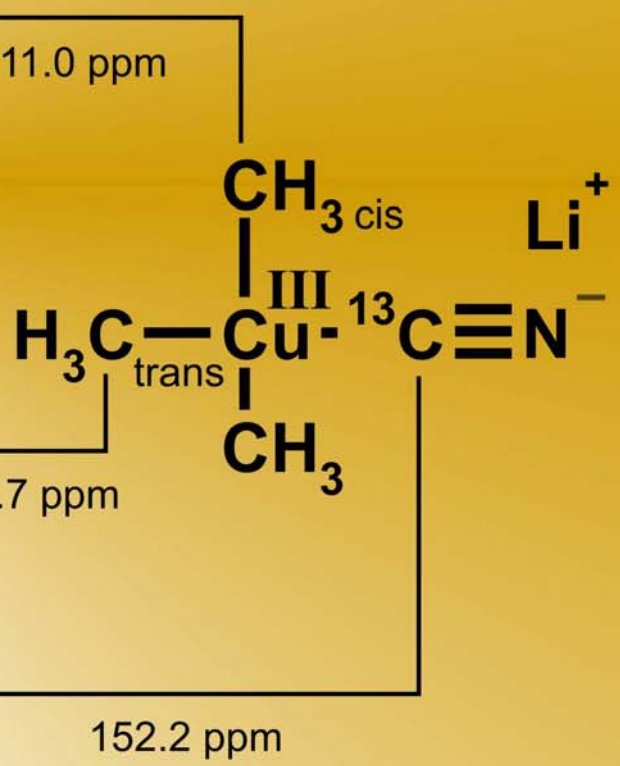


# NMR Detection of Cu(III)- Intermediates as Minor Species

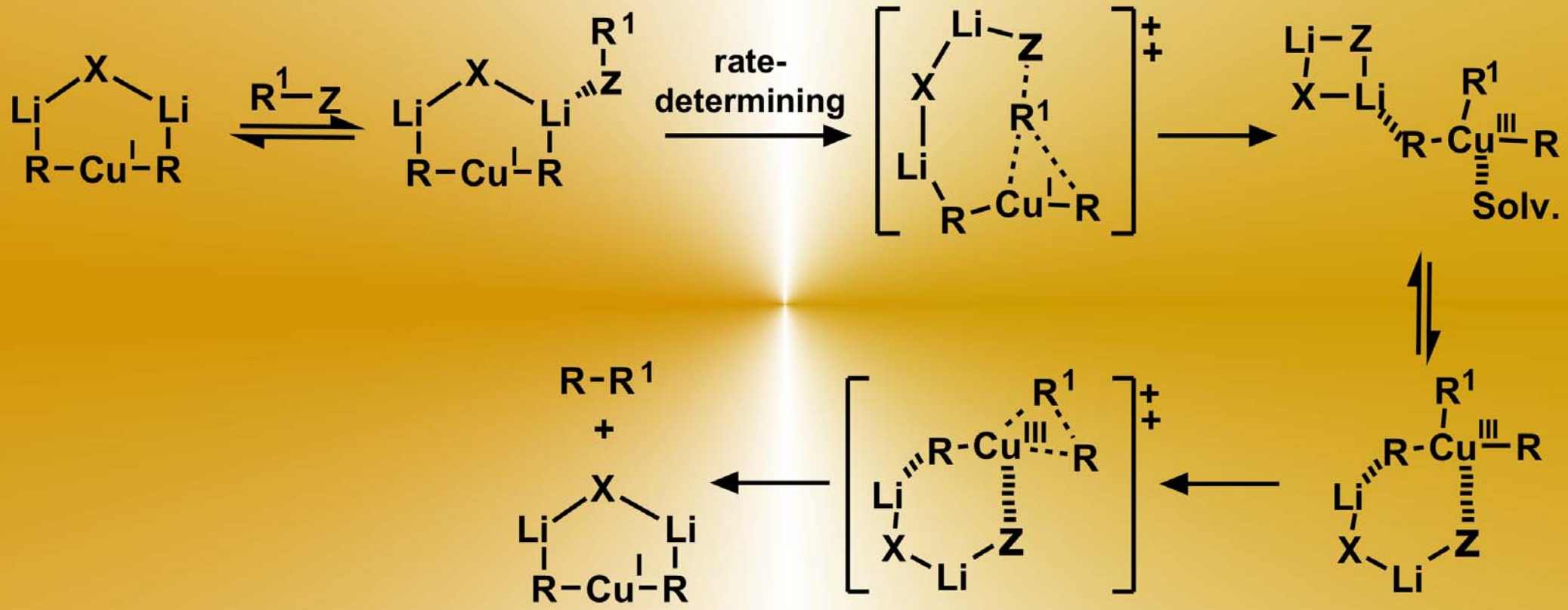



No contact to enone detectable in $^1$H,$^1$H-NOESY or $^1$H,$^{13}$C-HMBC



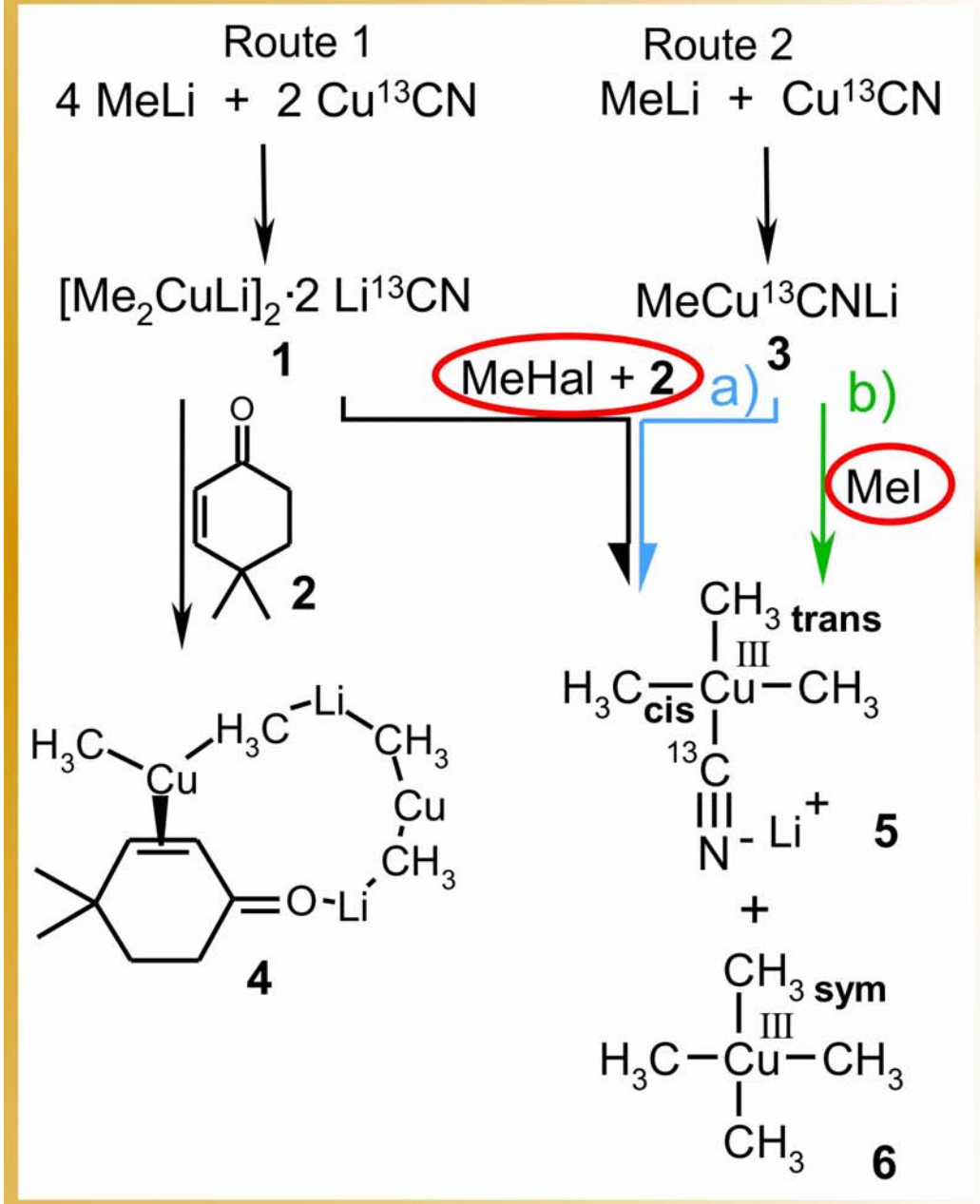

T. Gärtner, W. Henze, R. M. Gschwind, *J. Am. Chem Soc.* **2007**, *129*, 11362-3.

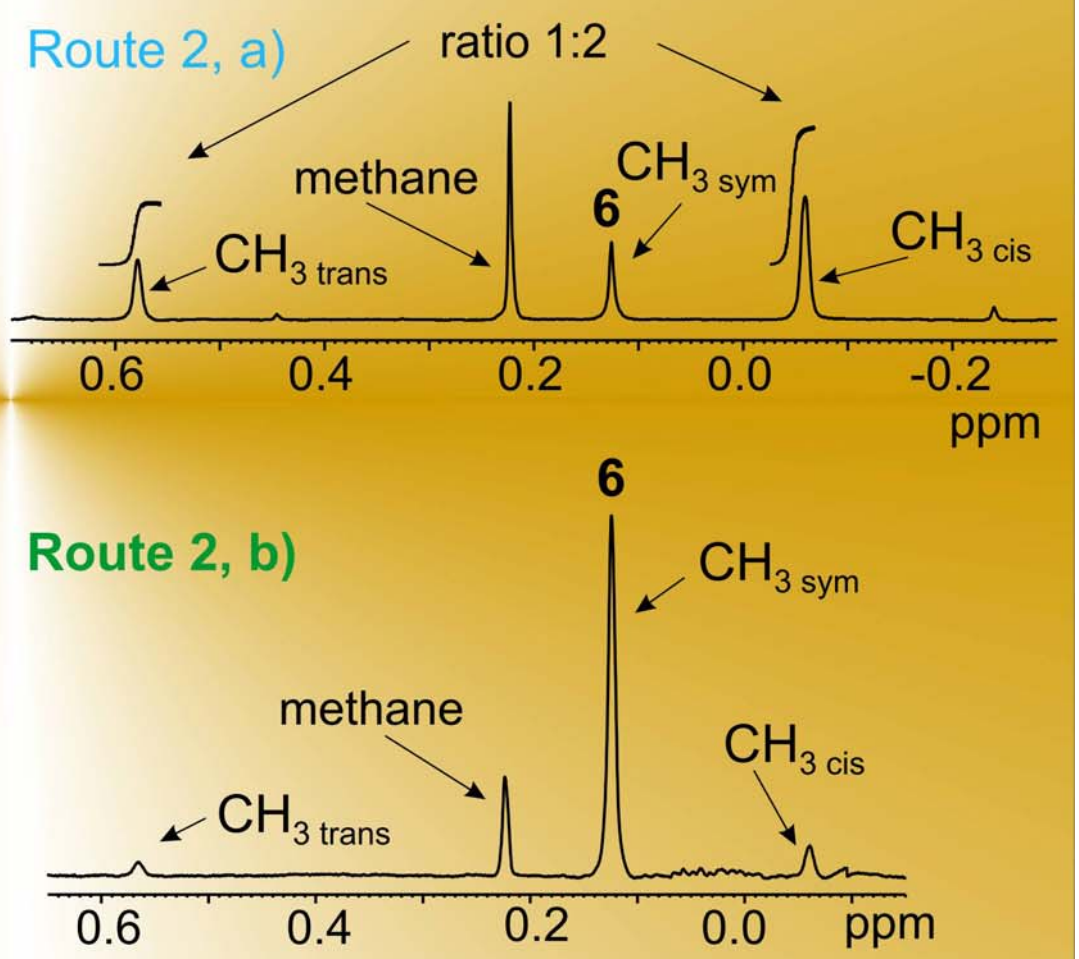
# Cu(III)-Species in Substitution Reactions




E. Nakamura, S. Mori, *Angew. Chem. Int. Ed.*, **2000**, *39*, 3750-71.

# Cu(III)-Intermediates

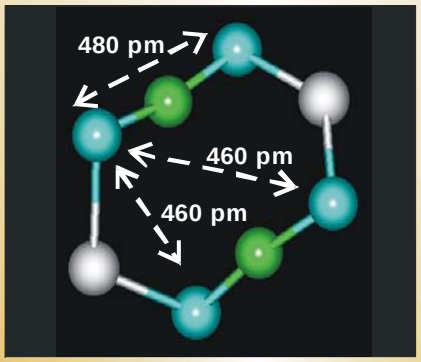


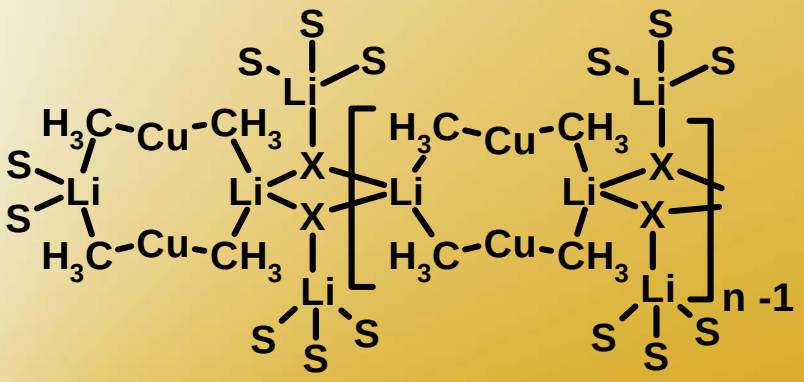




T. Gärtner, W. Henze, R. M. Gschwind, *JACS,* **2007**, *129*,11362-3.

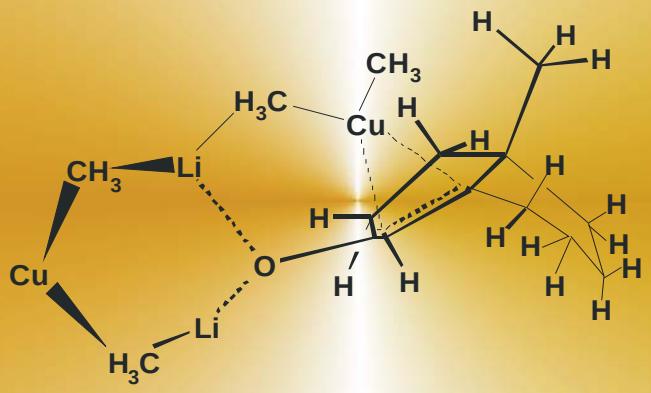
# Summary Part 1: Organocuprates

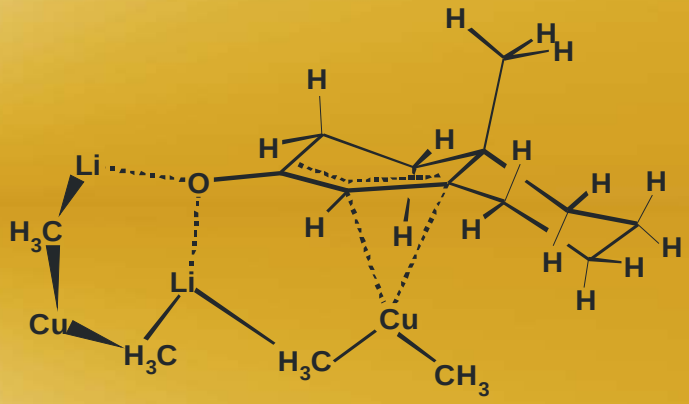
- Organocuprate reagents



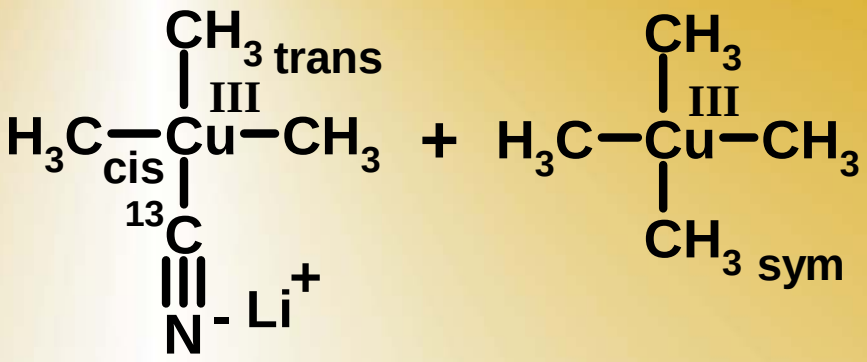




- Cu I Intermediates



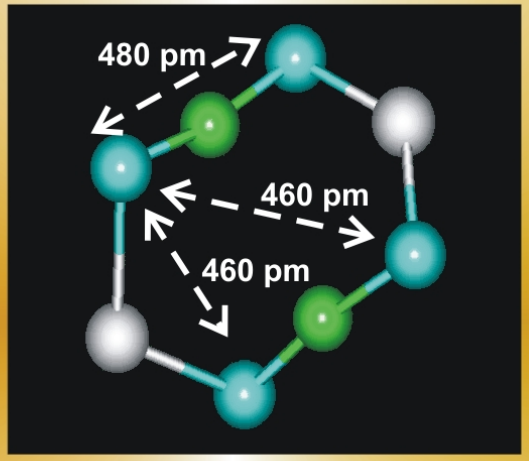

- Cu III Intermediates



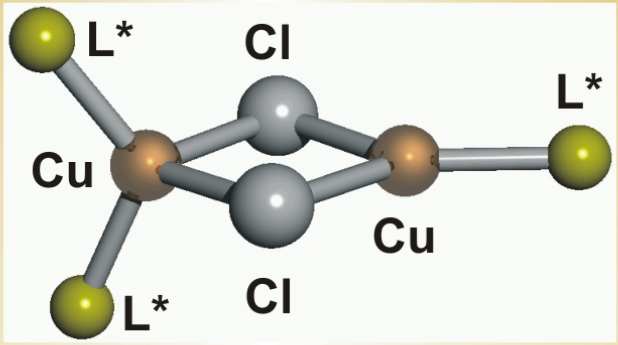
# Structure Elucidation of Copper Systems

R. M. Gschwind, *Chem. Rev.*, **2008,** *108*, 3029-53.

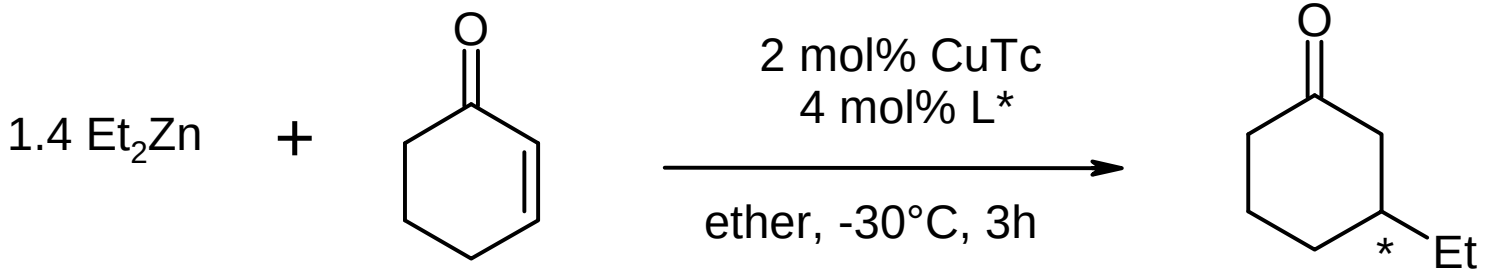
## Part 1: Organocuprate Reagents and Intermediates

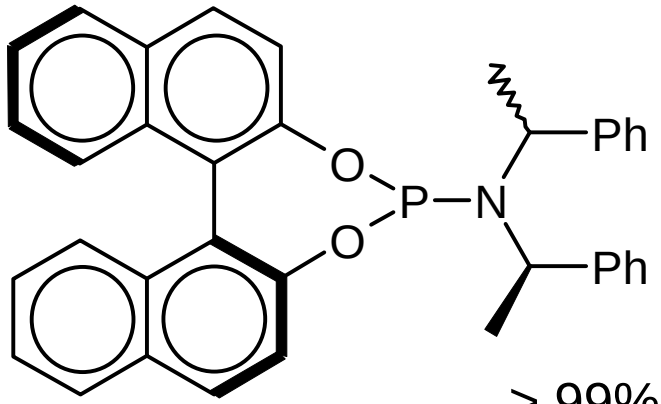



## Part 2: Precatalytic Copper Complexes in Enantioselective 1.4 Additions to Enones



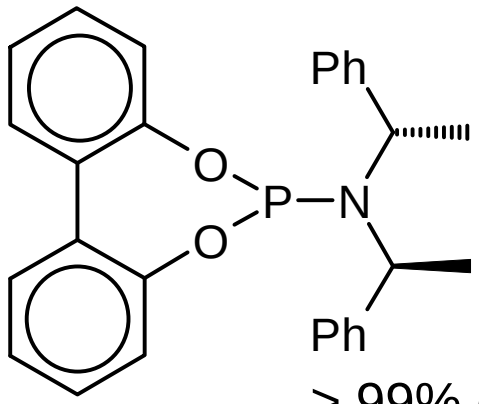
# Copper Cat. Enantioselective 1.4 Addition of $Et_2Zn$ to Enones




**1**

> 99% conversion
> 98% *ee*

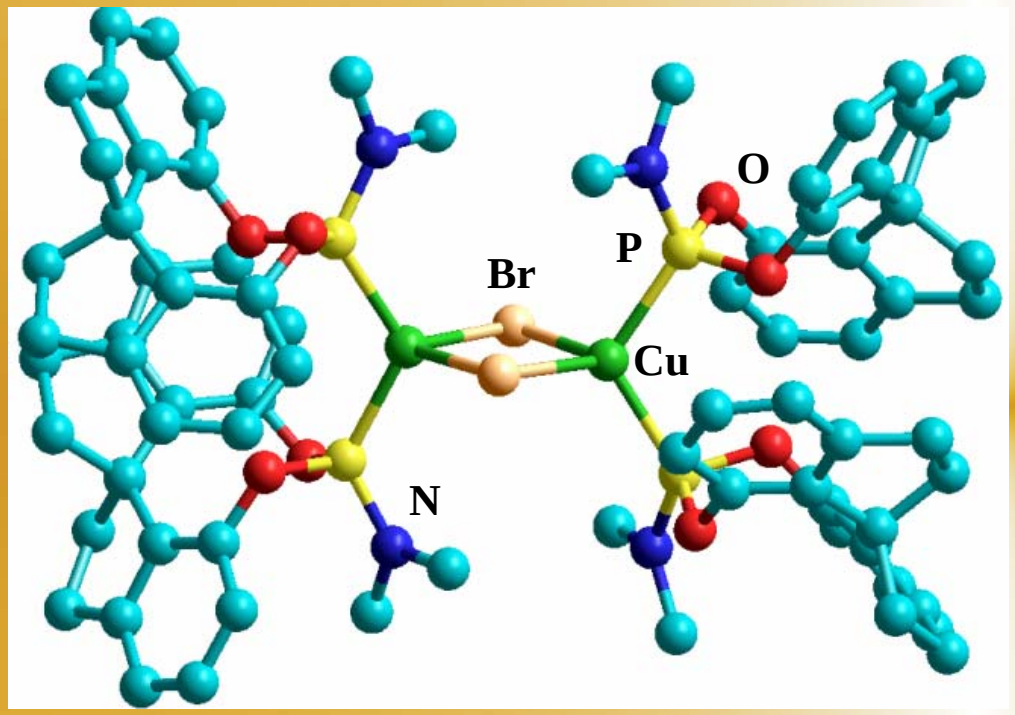



**2**

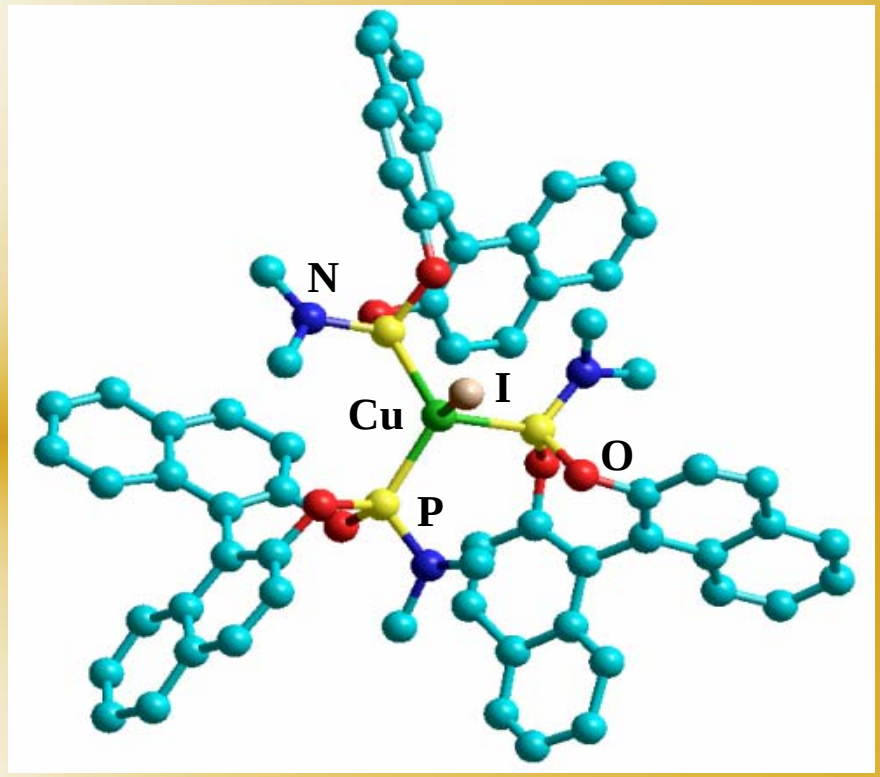
> 99% conversion
> 96% *ee*


A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221.
B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346.
A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262.

# Crystal Structures of Phosphoramidite Copper Complexes



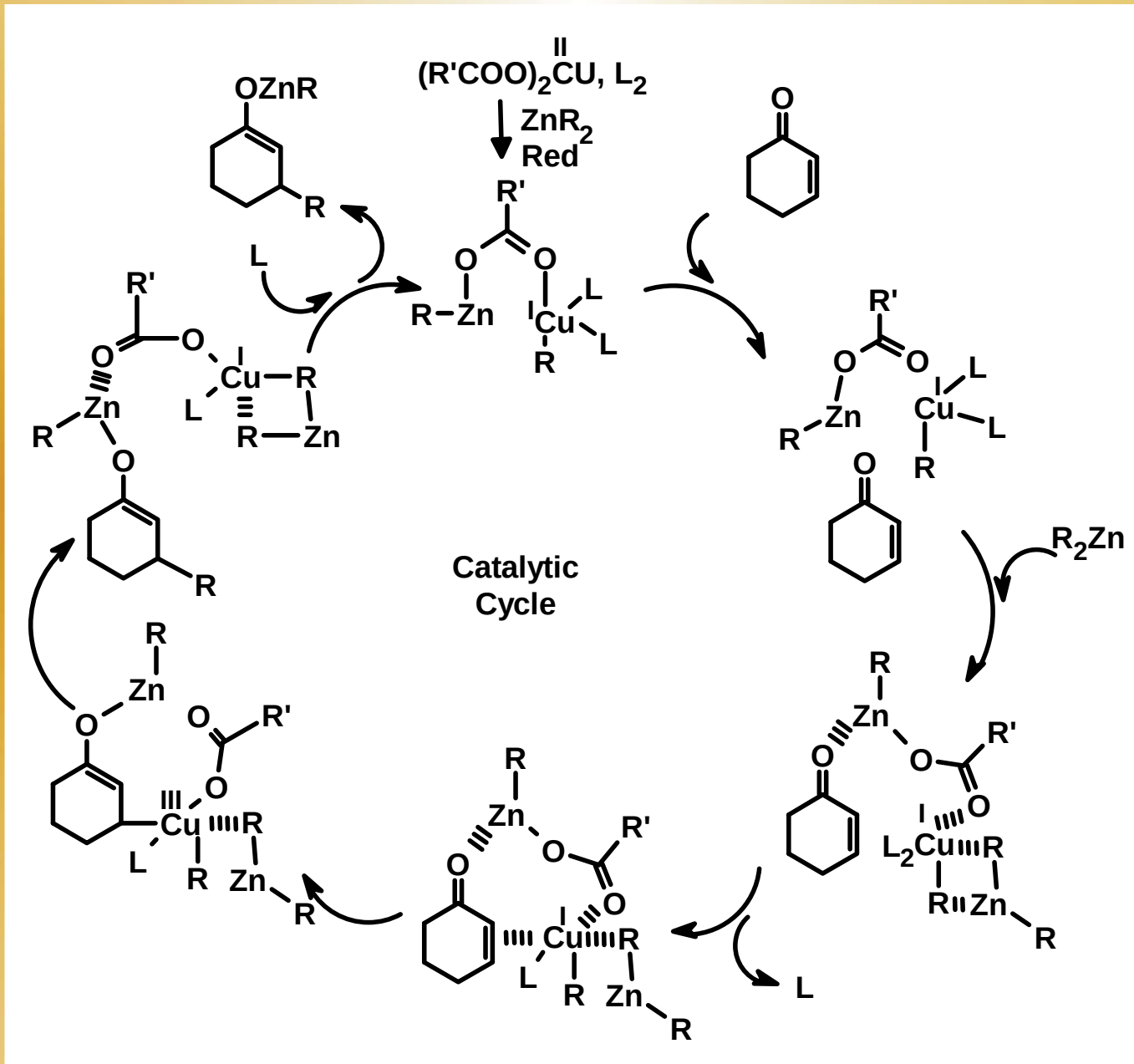

[CuBr(O,O´-(R)-(1,1´-Spirobiindane-7,7´-diyl)-N,N´-dimethylphosphoramidite)$_2$]$_2$




CuI(O,O´-(S)-(1,1´-Dinaphthyl-2,2´-diyl) – N,N´-dimethylphosphoramidite)$_3$

W. Shi, L. Wang, Y. Fu, S. Zhu, Q. Zhou, *Tetrahedron: Asymmetry* **2003**, *14*, 3867.
A. H. M. d. Vries, A. Meetsma, B. L. Feringa, *Angew. Chem. Int. Ed.* **1996**, *35*, 2374**.**

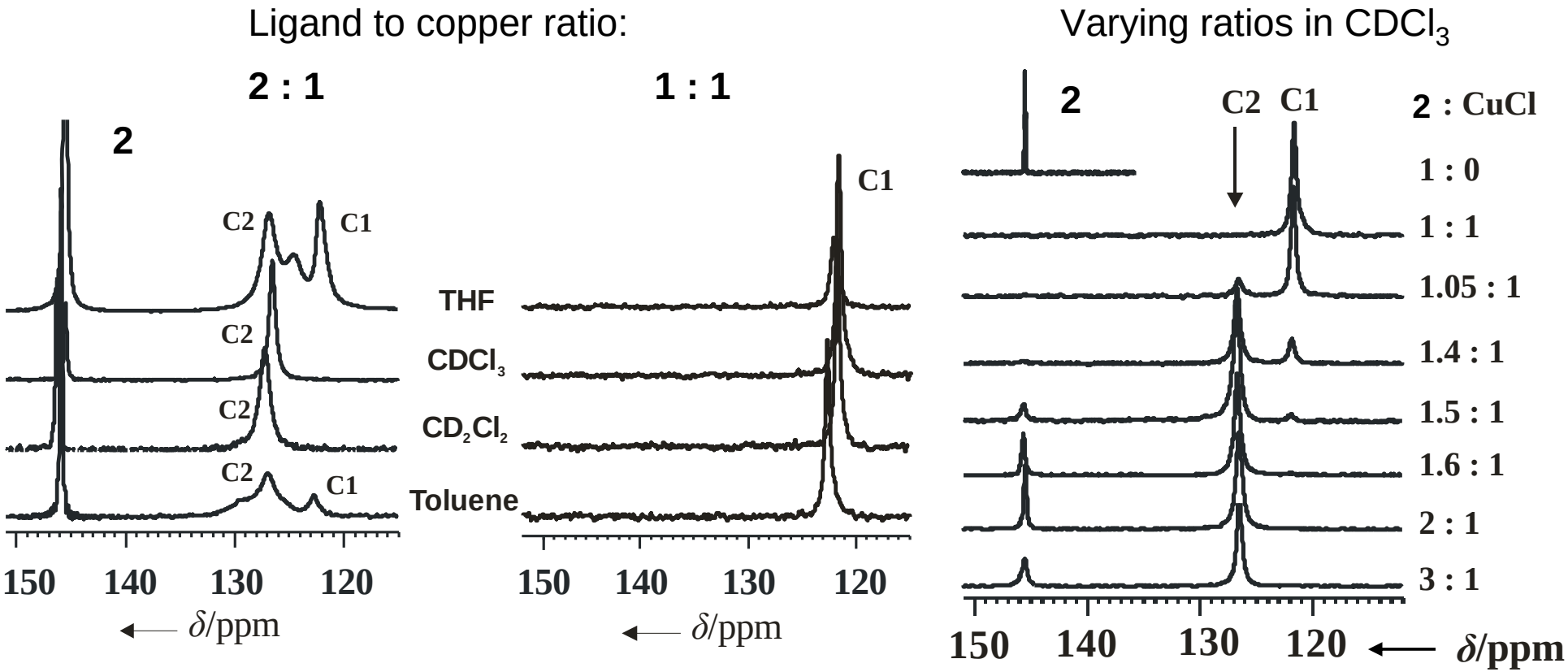
# One of the Proposed Catalytic Cycles




A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262**.**

# Identification of Precatalytic Copper Complexes via $^{31}$P-Spectra

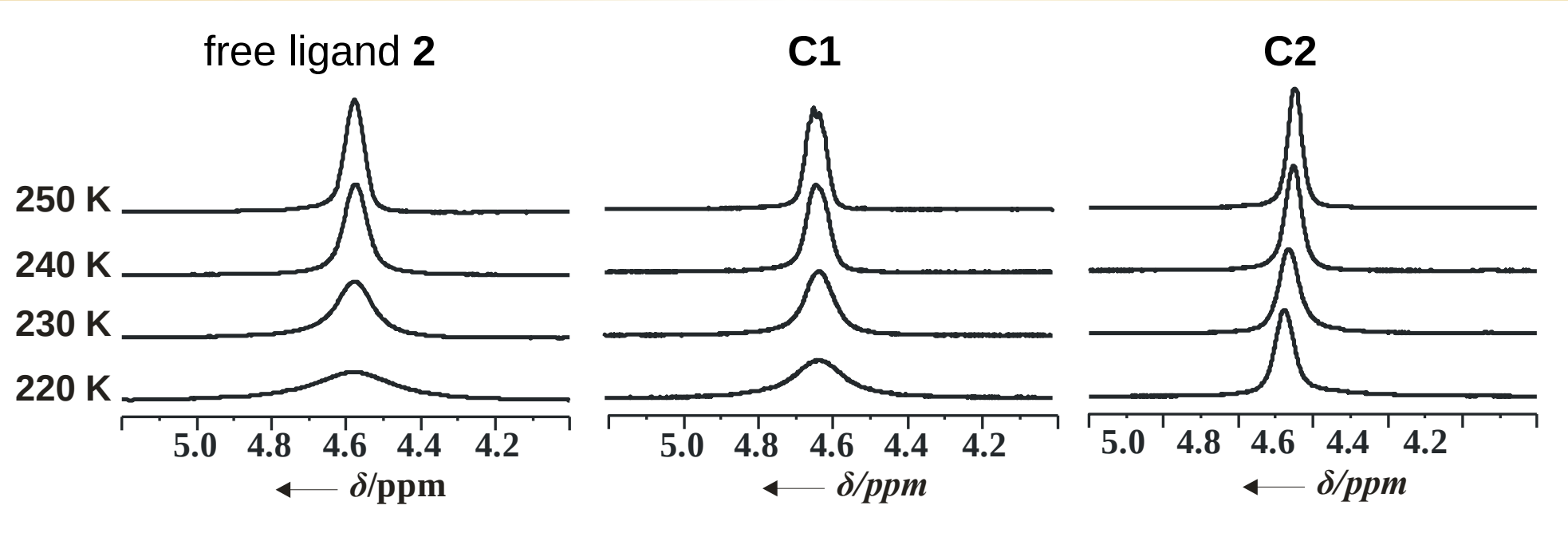
$^{31}$P-Spectra of Ligand **2** and CuCl at 220 K

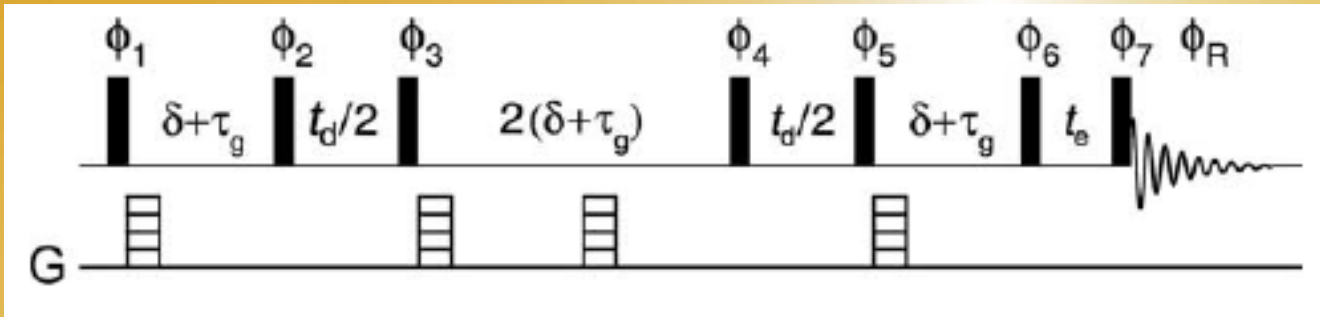



H. Zhang, R. M. Gschwind, *Angew. Chem. Int. Ed.*, **2006**, *45*, 6391-6394.

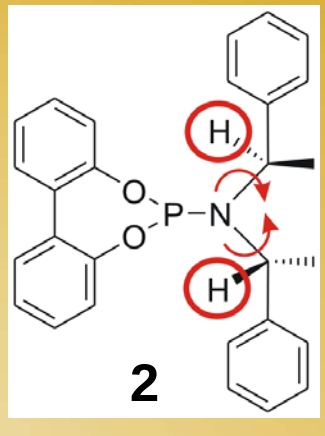
# Removal of $^1$H Signal Overlap via Internal Dynamic

$^1$H NMR spectra: Temperature dependence of the methine signal in



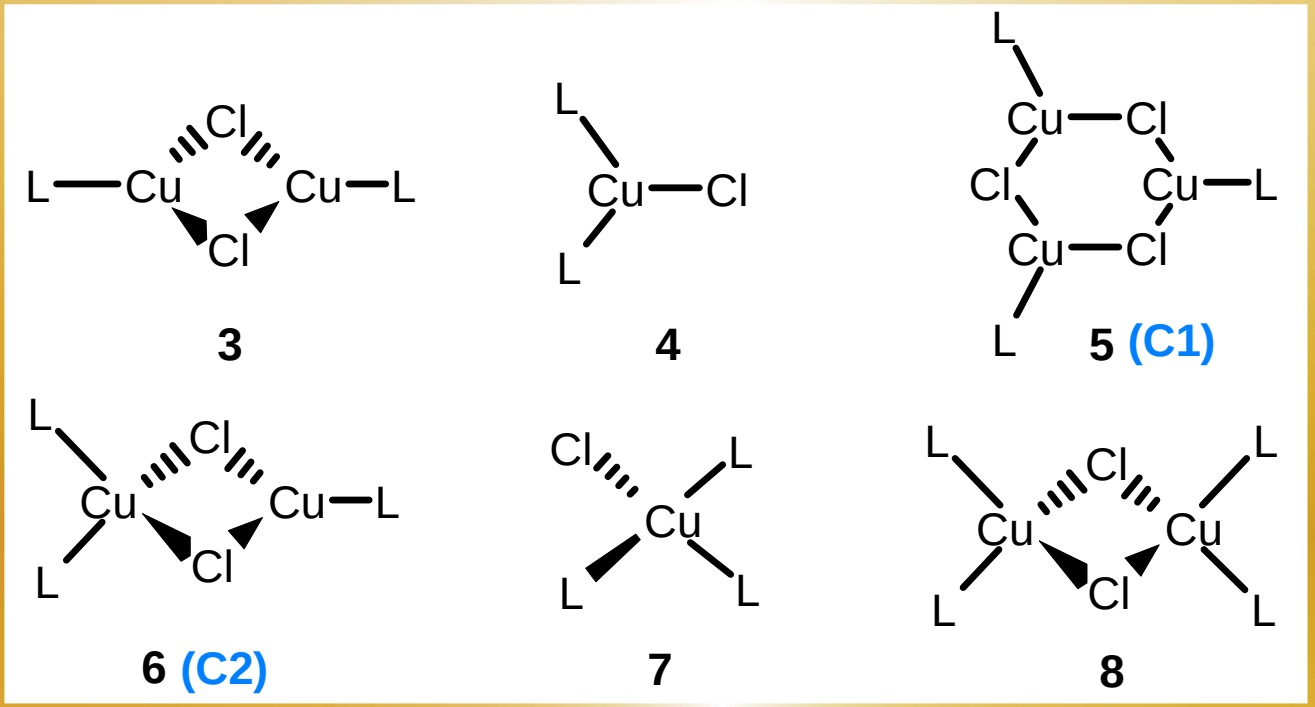

A. Jerschow, N. Müller, *J. Magn. Reson*. **1997**, *125*, 372.




**2**

# Number of Ligands from Model Complexes and Volumes

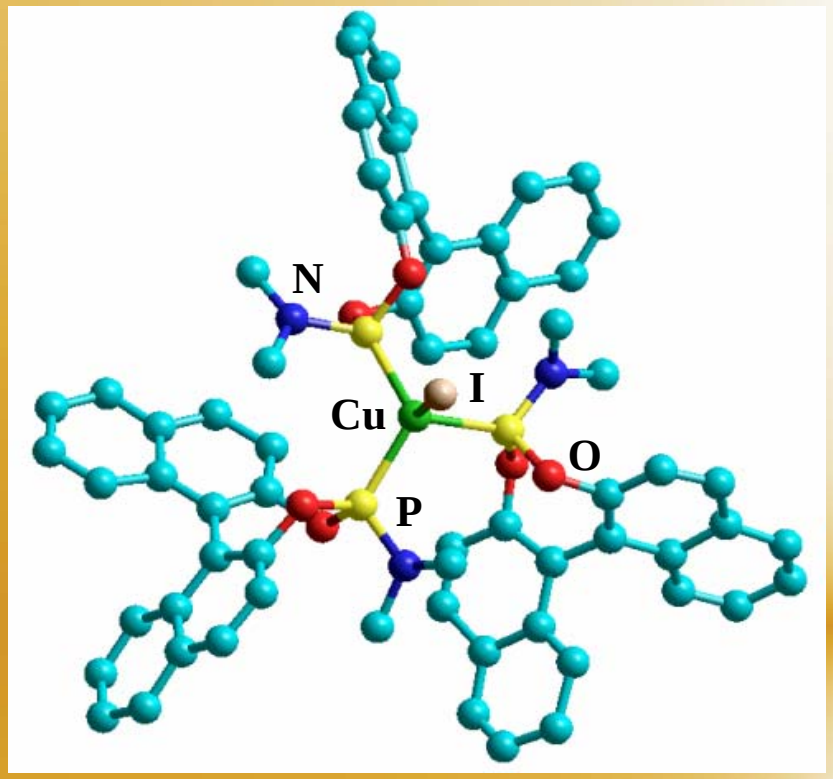
model complexes based on known X-ray structures

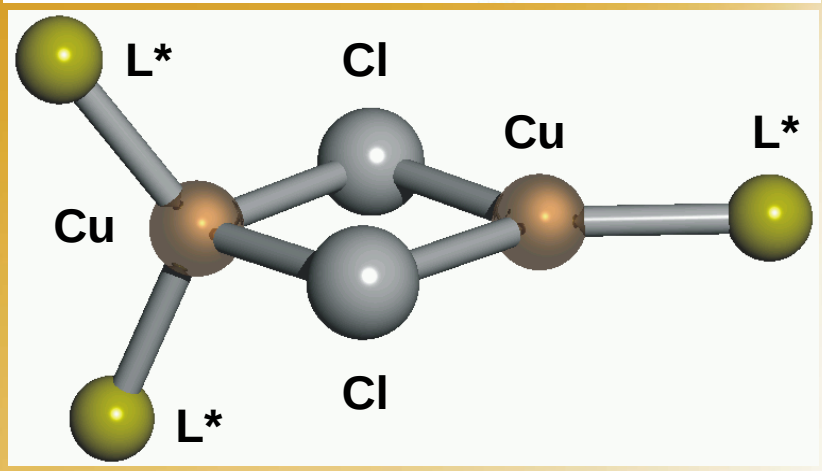


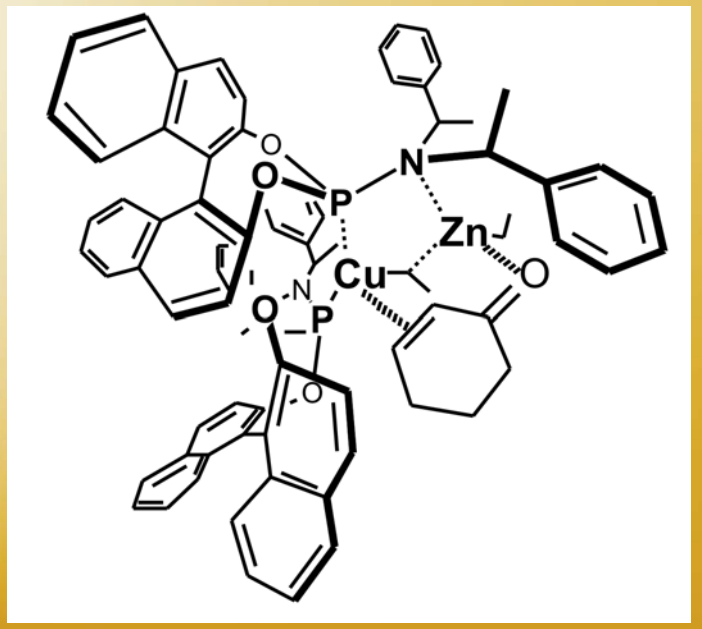

| exp. volumes | | | calc. volumes of the model complexes [Å$^3$] | | | | | |
|---|---|---|---|---|---|---|---|---|
| ligand | **C1** | **C2** | **3** (1:1) $L_2Cu_2Cl_2$ | **4** (2:1) $L_2CuCl$ | **5** (1:1) $L_3Cu_3Cl_3$ | **6** (1.5:1) $L_3Cu_2Cl_2$ | **7** (3:1) $L_3CuCl$ | **8** (2:1) $L_4Cu_2Cl_2$ |
| **1** | **2305** | **2228** | 1595 | 1565 | **2393** | **2363** | **2333** | 3131 |
| **2** | **1588** | **1525** | 1018 | 989 | **1528** | **1498** | **1468** | 1977 |

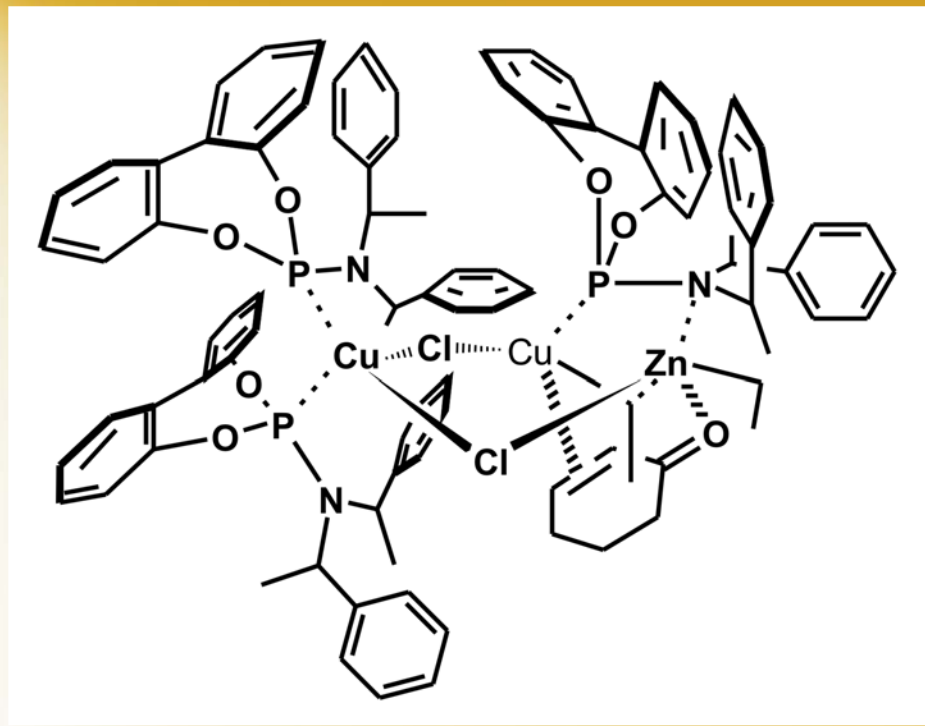
H. Zhang, R. M. Gschwind, *Angew. Chem. Int. Ed.*, **2006**, *45*, 6391-6394.

# From Precatalytic Cu-Complexes to Intermediates

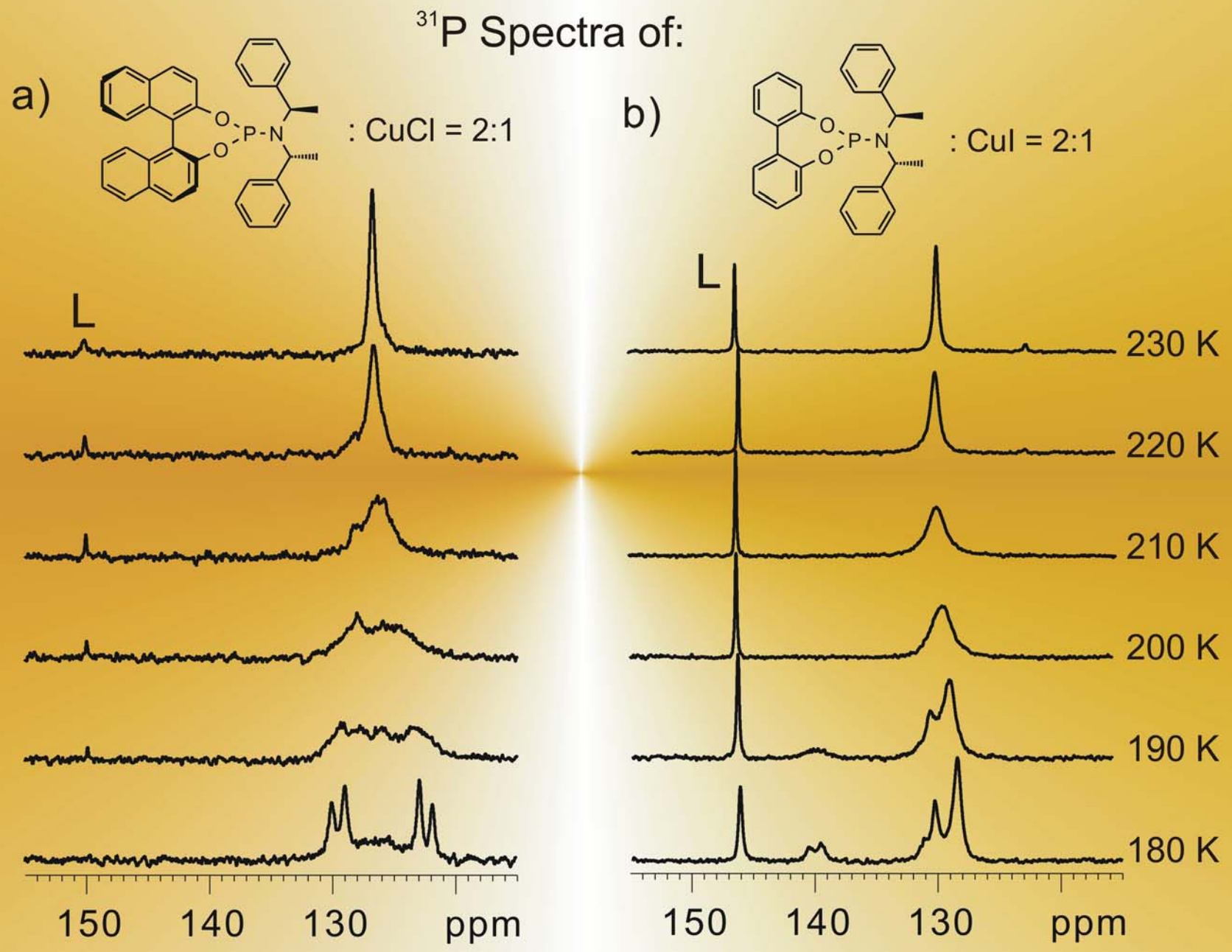


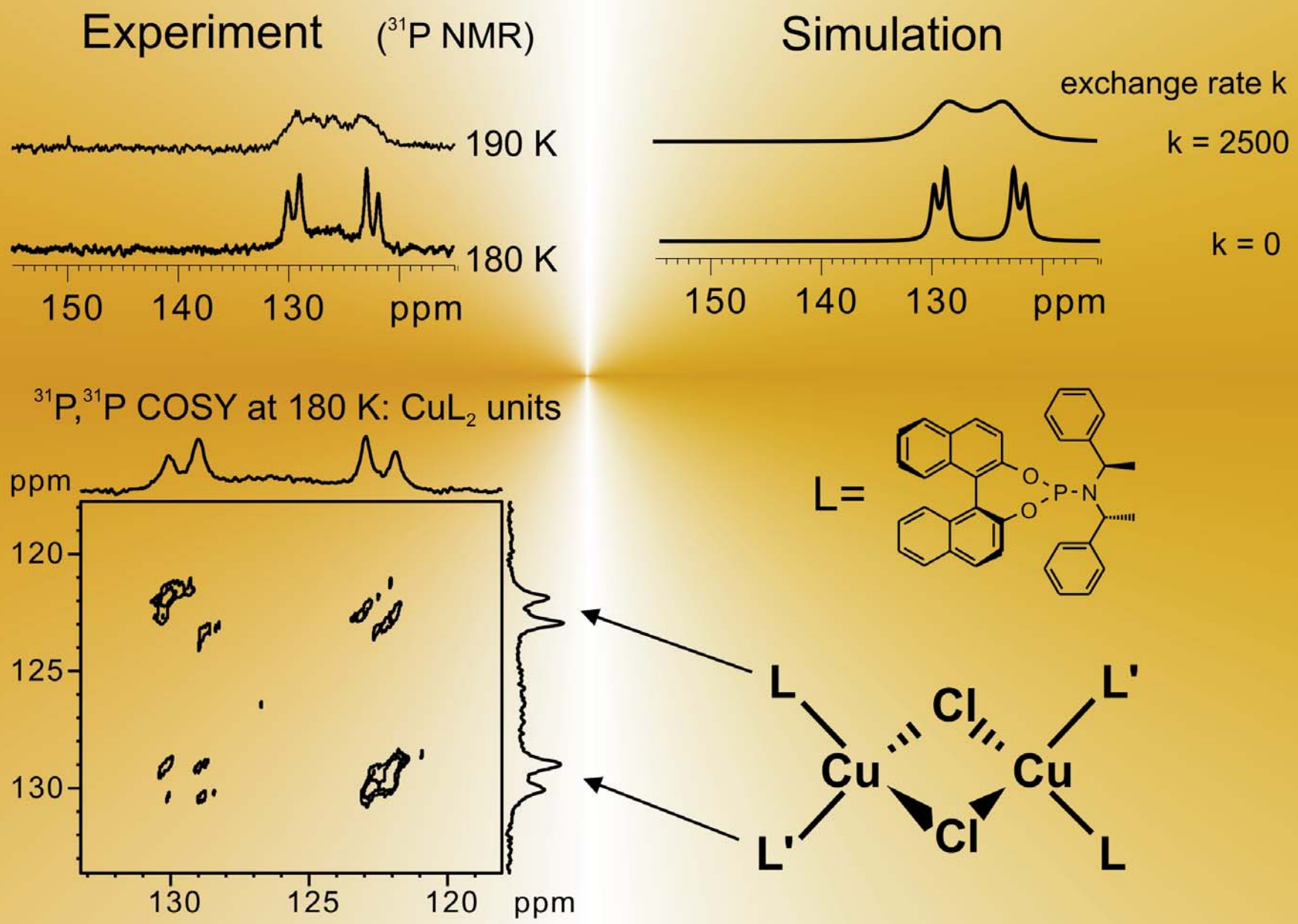



# Temperature Influence on Precatalytic Complexes

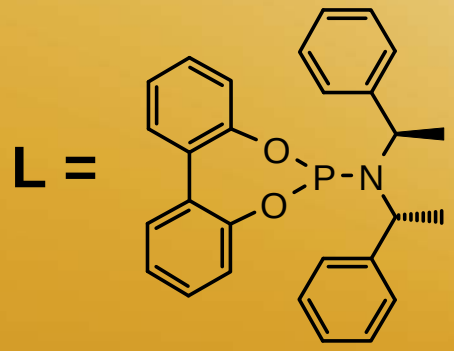


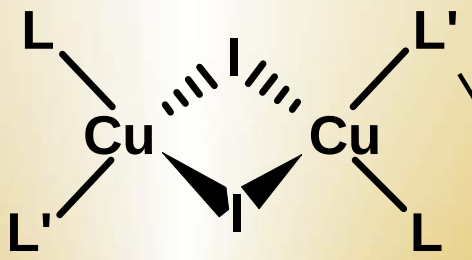

K. Schober, H. Zhang, R. M. Gschwind, *J. Am. Chem. Soc.*, **2008**, *130*, 12310-12317.

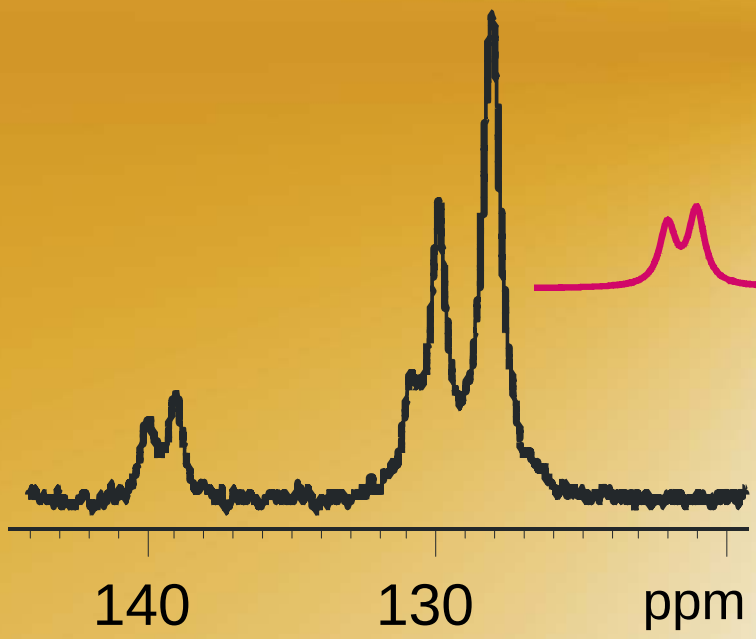
# Simulations and $^{31}P,^{31}P$ COSY Indicate AA' BB' Spinsystems in Binuclear $[L_2CuX]_2$ Complexes



# Identification of Second Low Temperature Species at 180 K



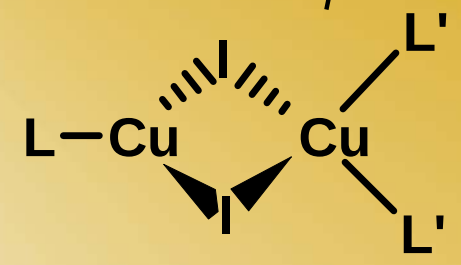




experimental $^{31}$P NMR spectrum

superposition

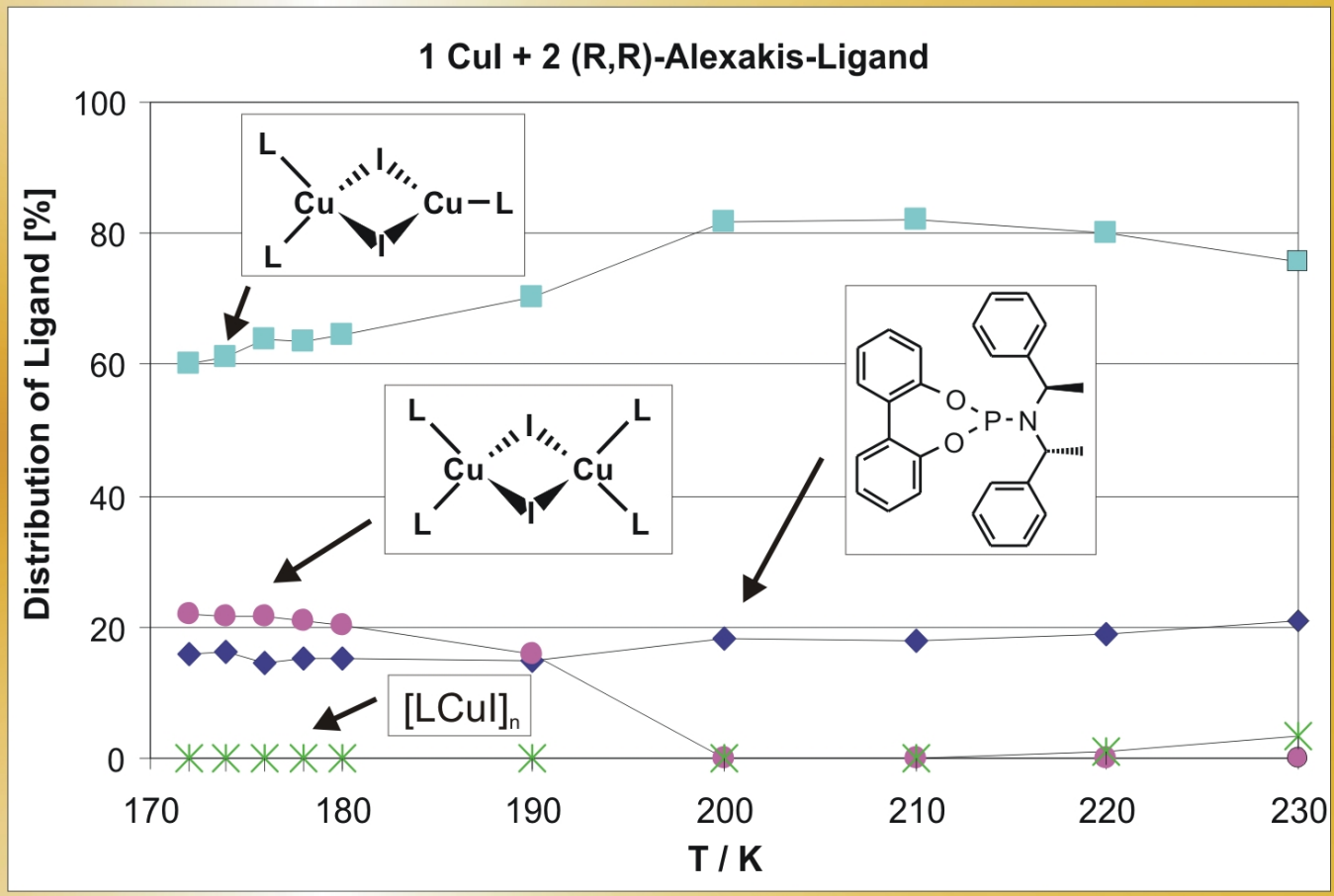
simulation

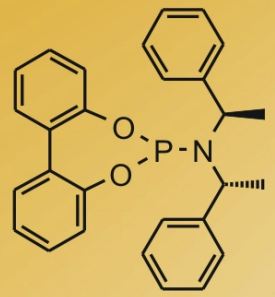
+ simulation



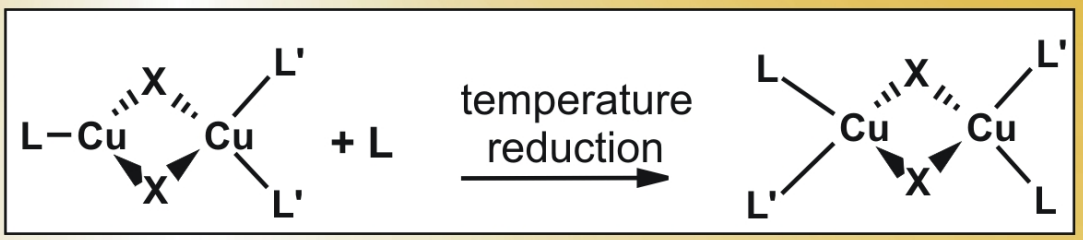

K. Schober, H. Zhang, R. M. Gschwind, *J. Am. Chem. Soc.*, **2008**, *130*, 12310-12317.

# $^{31}$P Integrals Monitor
# Temperature Dependent Interconversion of Cu Complexes

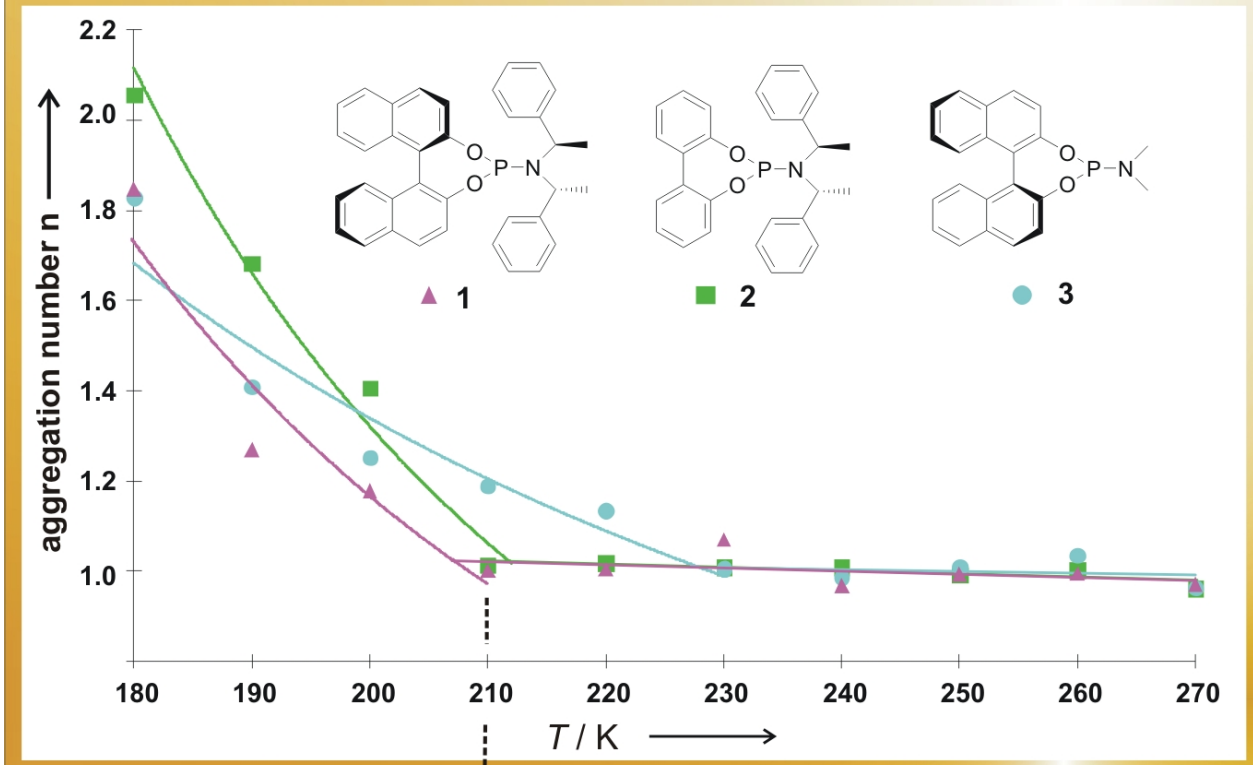



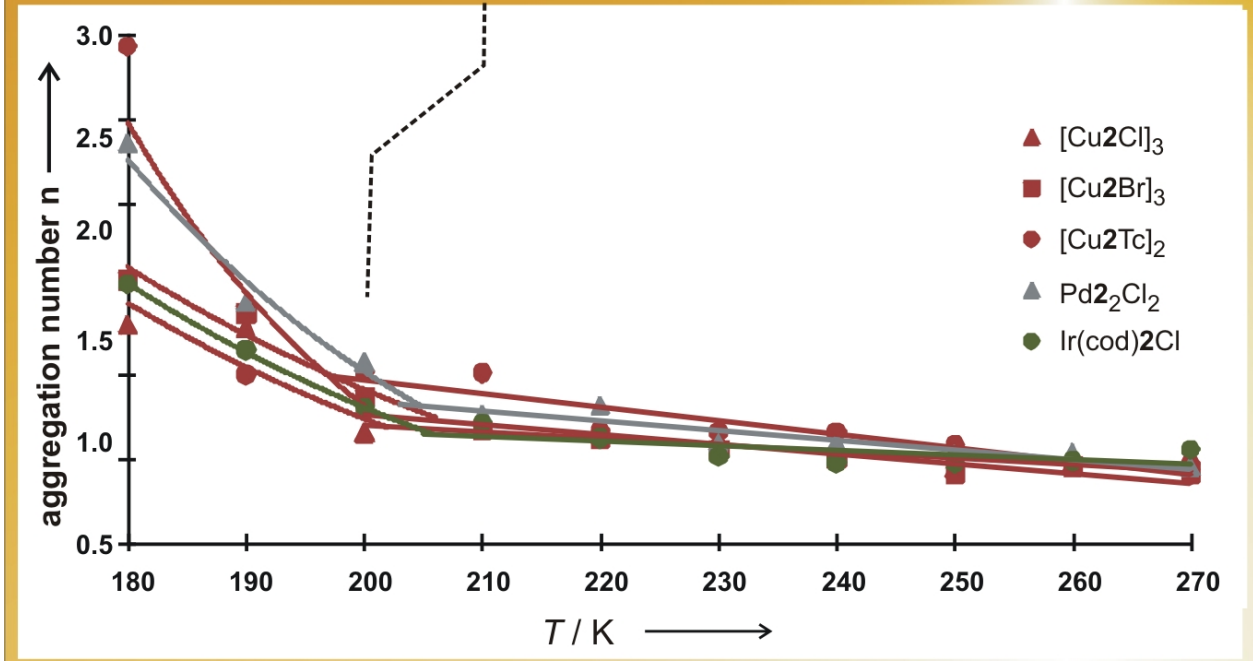




+ CuI

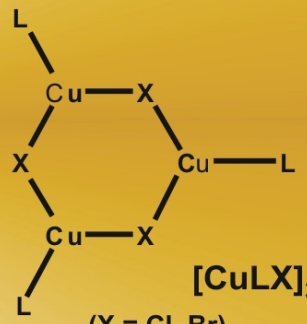


# Ligands as Easy Sensors of the Aggregation of Complexes




## Aggregation with Ligand 2

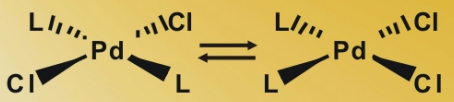



$[CuLX]_3$

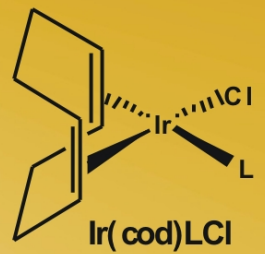
(X = Cl, Br)


$[CuLX]_2$

(X = Tc)




$PdL_2Cl_2$



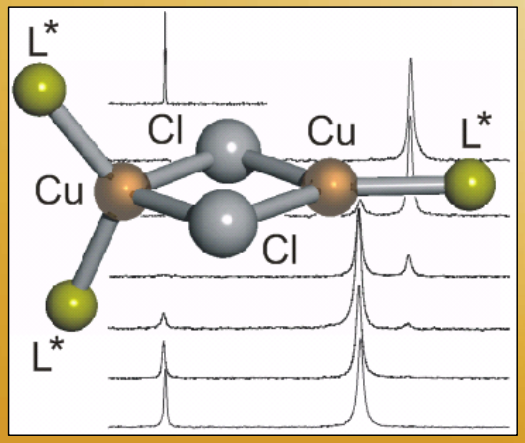

Ir(cod)LCl

Temperature dependent aggregation of $[CuLX]_3$ (X = Cl, Br, TC), $PdL_2Cl_2$ and Ir(cod)LCl
L = **2**, in $CD_2Cl_2$ (0.02 M)
based on the $\eta/T$-corrected diffusion coefficients.

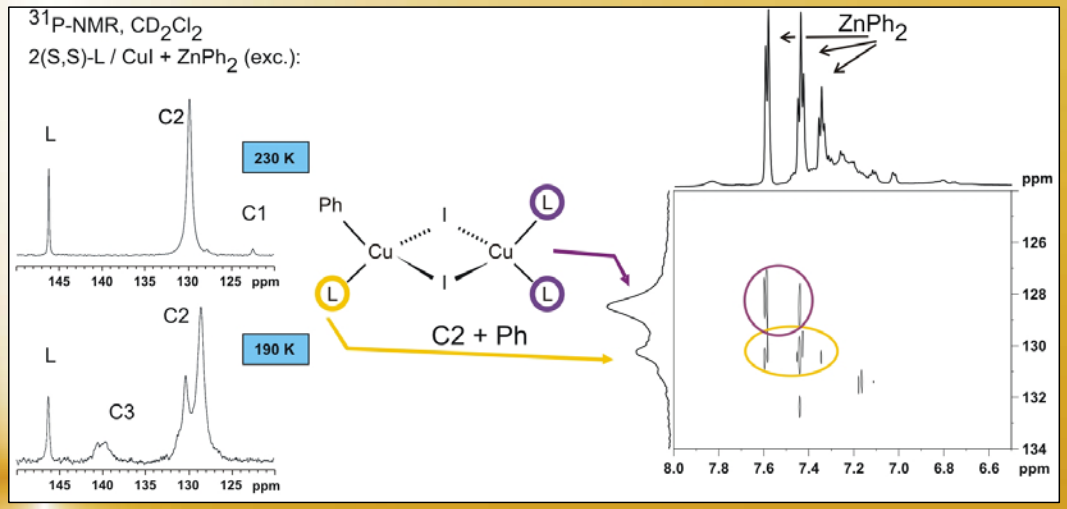
K. Schober, E. Hartmann, H. Zhang, R. M. Gschwind, *Angew. Chem.*, **2010**, *accepted*.

# Summary Part 2

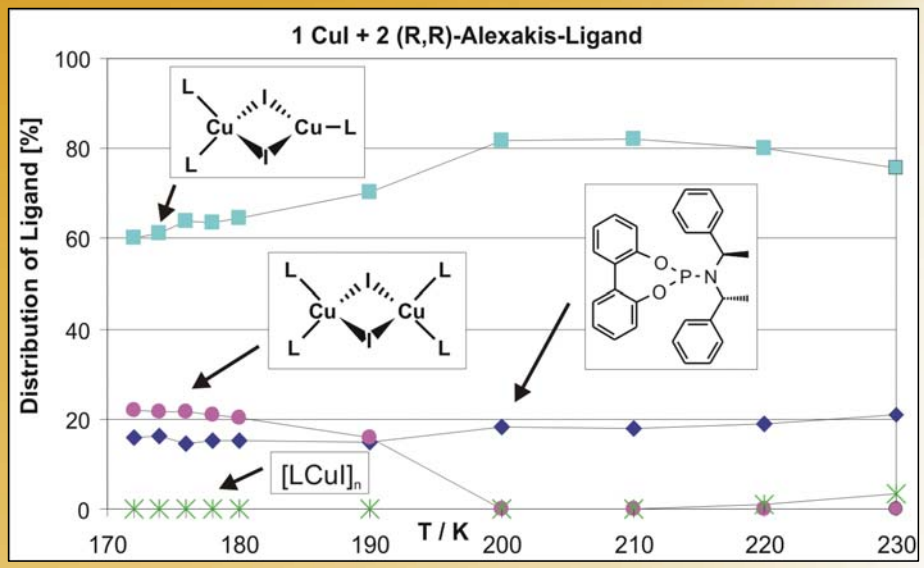
- new precatalytic structure



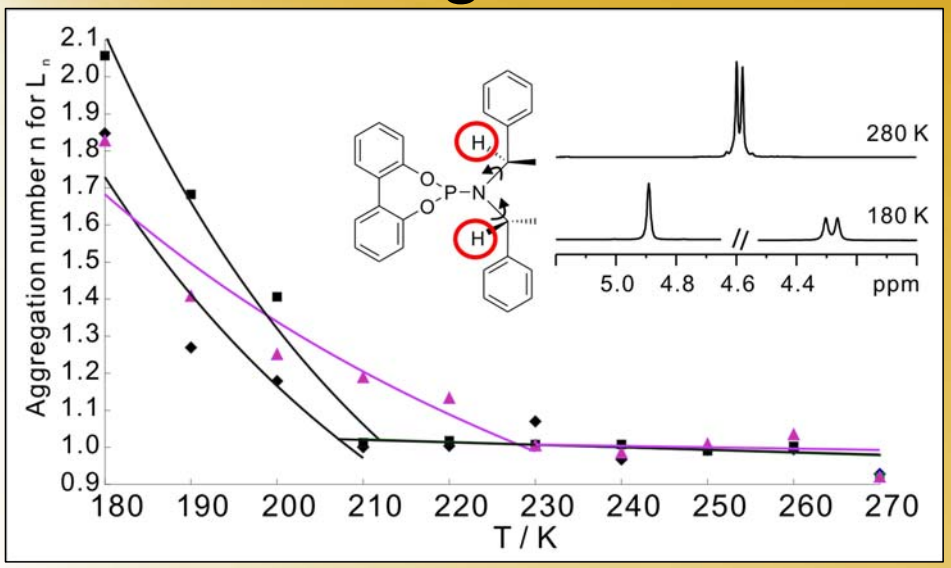

- transmetallated intermediate



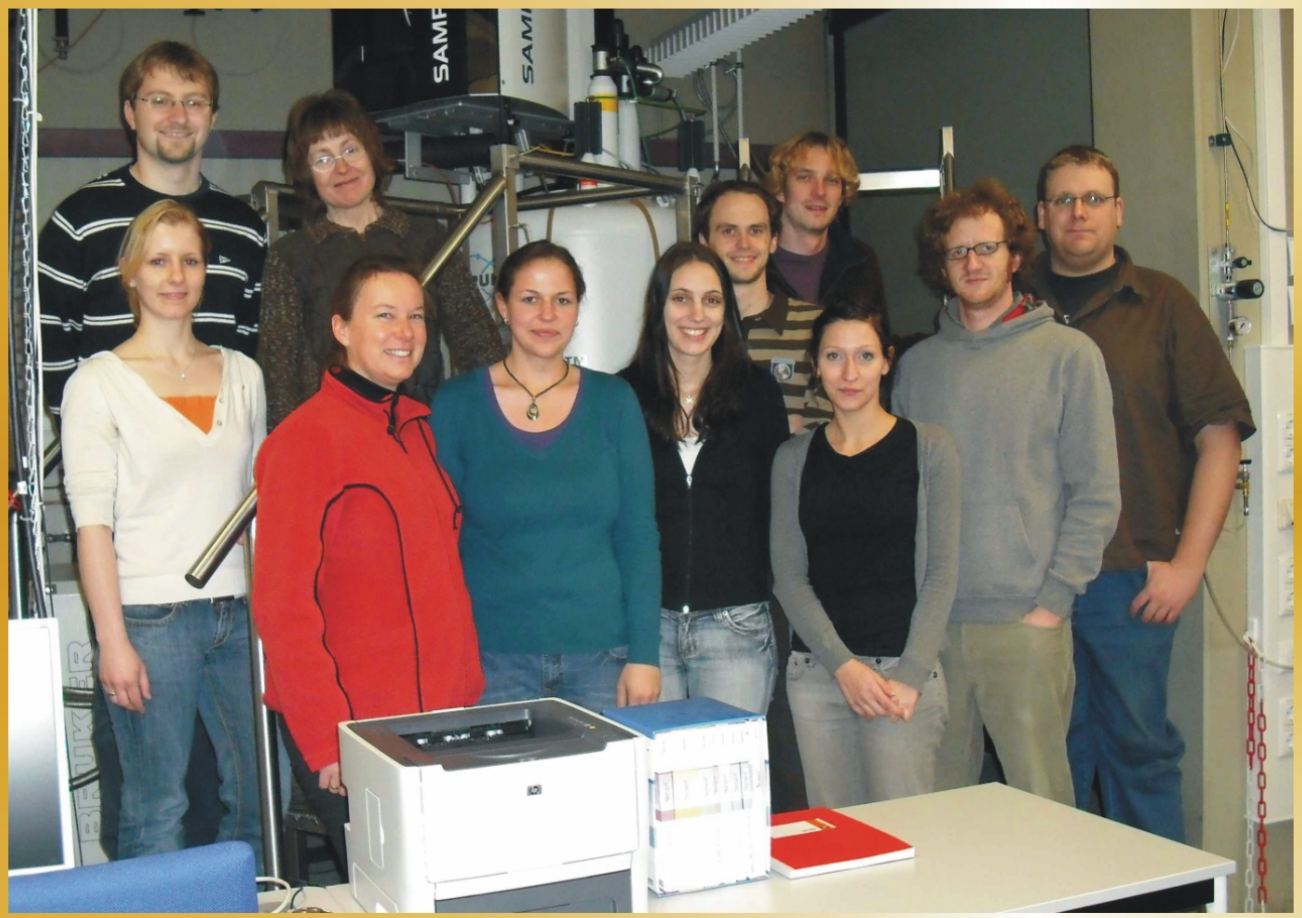

- temperature dependent interconversion




- new aggregation screening method



# Acknowledgement



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