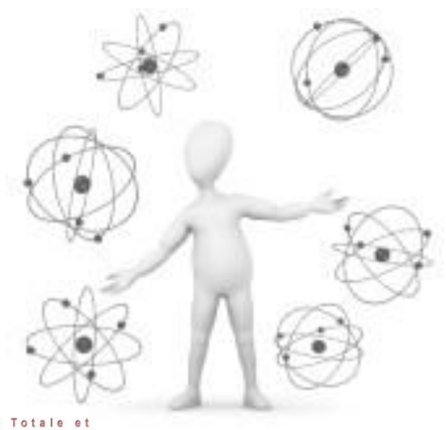
Kinetic Isotope Effects for Mechanism Elucidation and Total Synthesis

Group Meeting 25/11/2013

Jérémy Merad

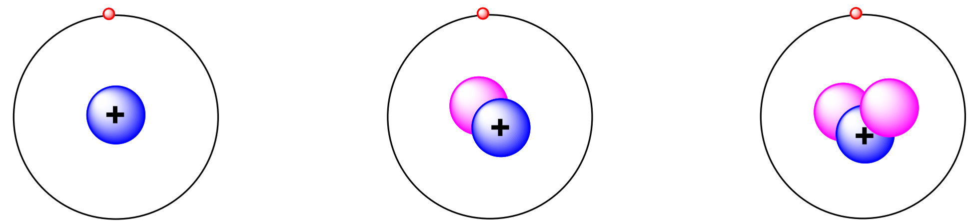


Aix*Marseille université

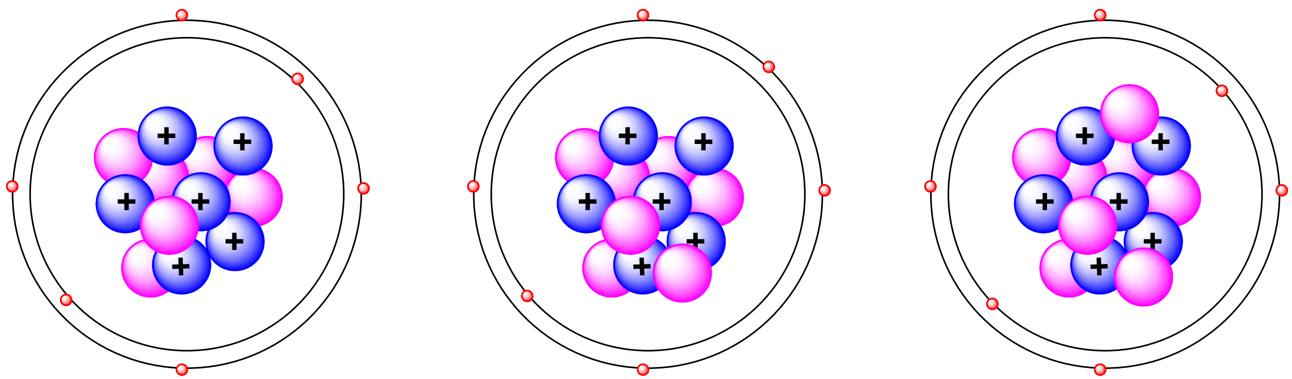
iSm2 Institut des Sciences Moléculaires de Marseille UMR 7313

Synthèse Totale et StéRéO Réactivité Organique

What's Isotope ??



Hydrogen ^{1}H | Deuterium ^{2}H | Tritium ^{3}H



Carbon ^{12}C | Carbon ^{13}C | Carbon ^{14}C

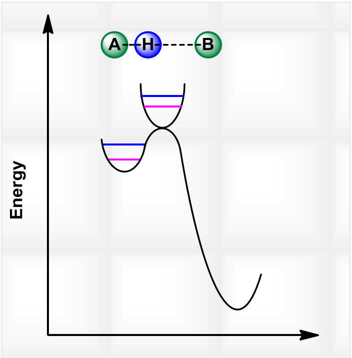
Same number of protons and electrons
Same chemical properties
≠ number of neutrons
≠ atomic mass

A Useful Object

NMR Analysis

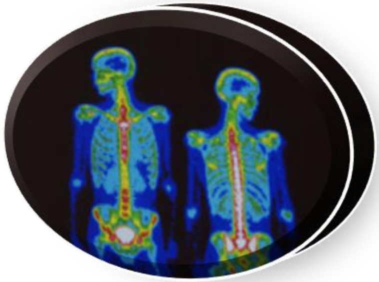
Nuclear Field

Organic Datation



Reaction Mechanism

Organic Synthesis



Medical Imagery

An Old Story

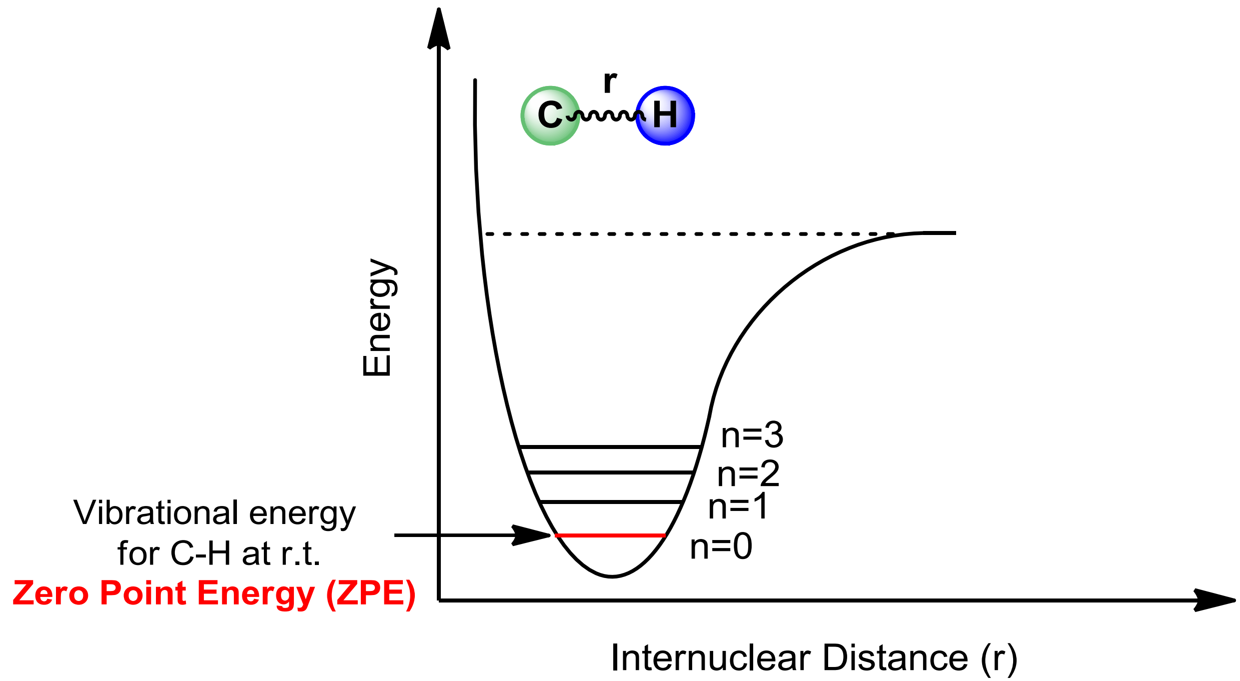
- **1919 -** ***Francis W. Aston discovered isotopes***
  Nobel Prize of Chemistry in 1922
- **1927 -** ***He determined the atomic weight of hydrogen***
- **1929 -** ***W. F. Giauque and H. W. Johnston proved than ordinary oxygen contained ^{17}O and ^{18}O***
- **1932 -** ***H. C. Urey reported the existence of heavy hydrogen which he named deuterium and heavy water (D_2O) - Then, he described the enrichment of D in water by electolysis***
  Nobel Prize of Chemistry in 1934
- **1933 -** ***G. N. Lewis and R. T. MacDonald reported the isolation of a small quantity of heavy water by distillation***
- **1934 -** ***More than 200 papers described the use, isolation and properties of deuterium.***

Isotope Effects : Theoretical Approach

And

Use in Mechanism Explorations

Isotope Effect : a Physical Origin

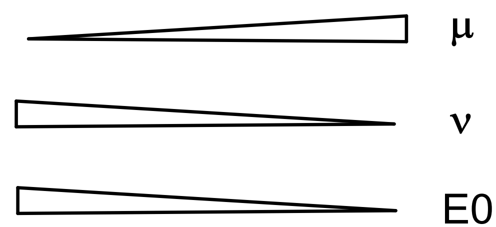


Harmonic oscillator approximation

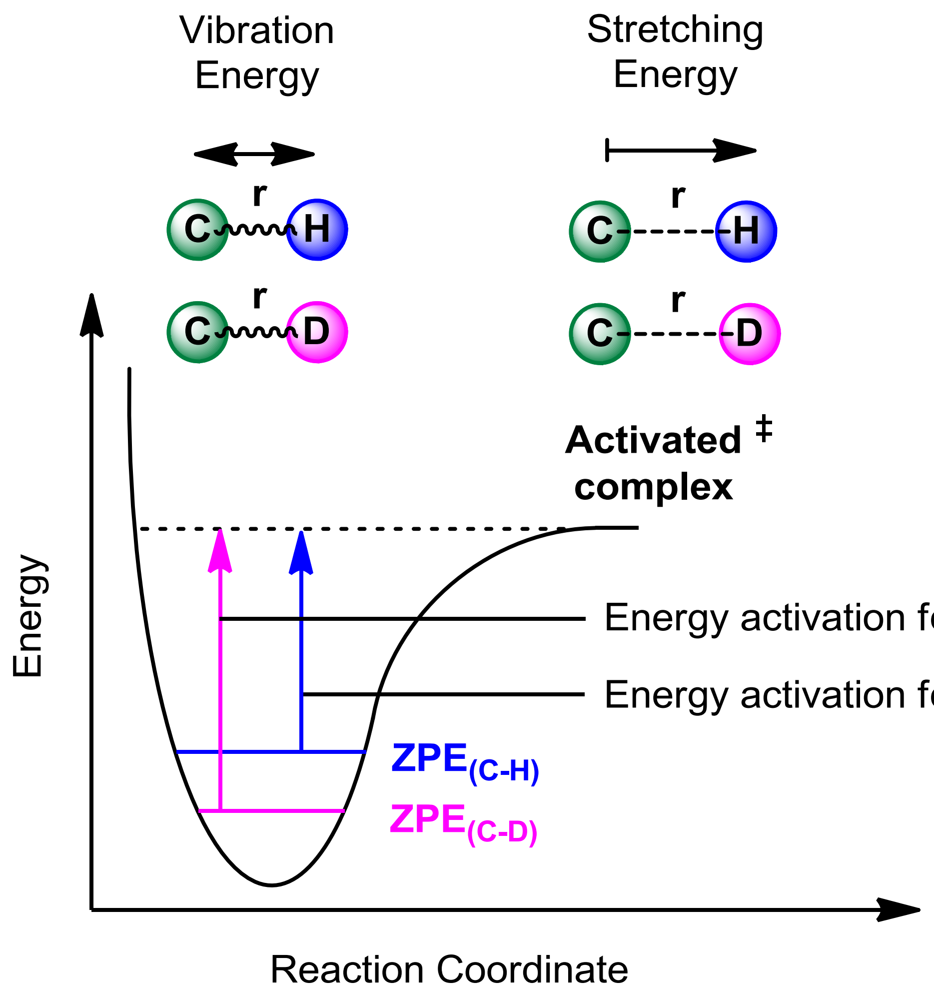
$$En = (n - 1) \,.\, h\nu$$

$$\nu = \frac{1}{2\pi \,.\, c}\sqrt{\frac{k}{\mu}}$$

$$\mu = \frac{m1 \,.\, m2}{m1 + m2}$$



The Eyring Theory of Absolute Rates



$\Delta G_{C-H} - \Delta G_{C-D} > 0$

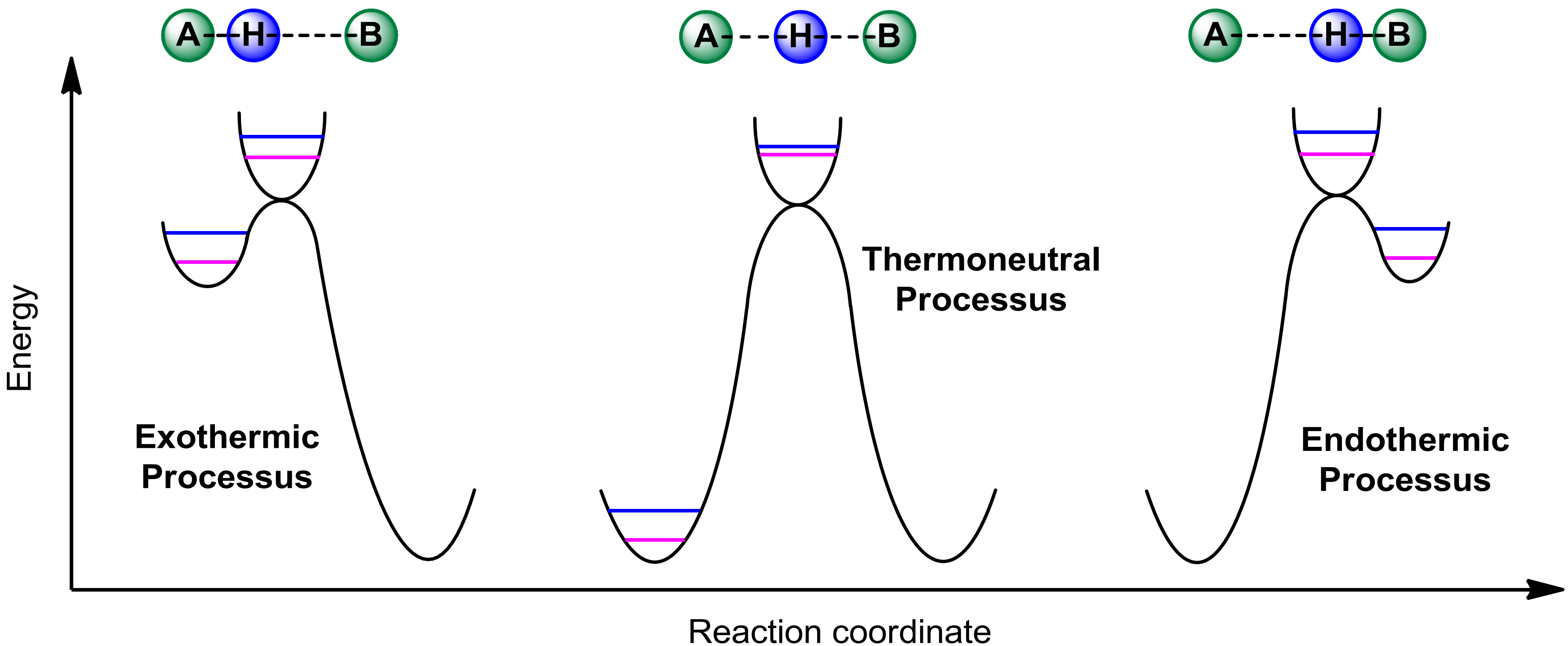
⇩

k_H / k_D = KIE ~ 7
if C-H bond is broken during the rate-determining step

Bond Type	μ	ZPE (kcal.mol^{-1})
C-H	0.92	4.15
C-D	1.71	3.00

H. Eyring, A. J. Sherman, *Chem. Phys.*, **1933**, *1*, 435

The Westheimer Model - Hammond Postulat

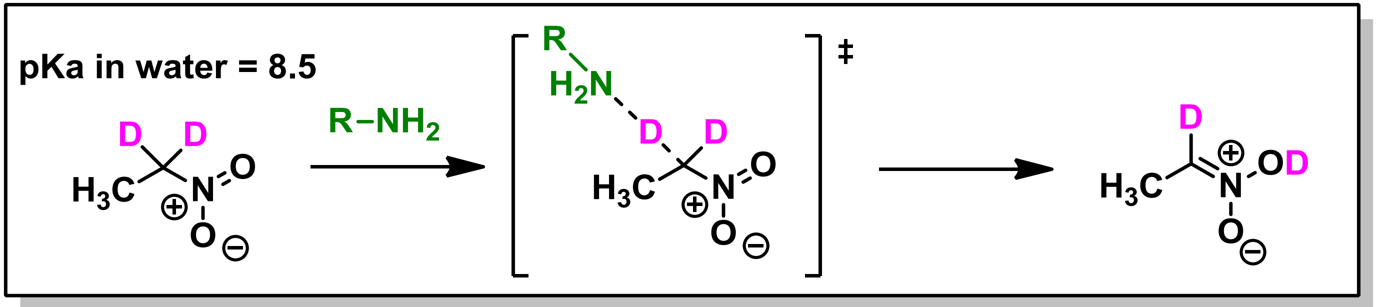


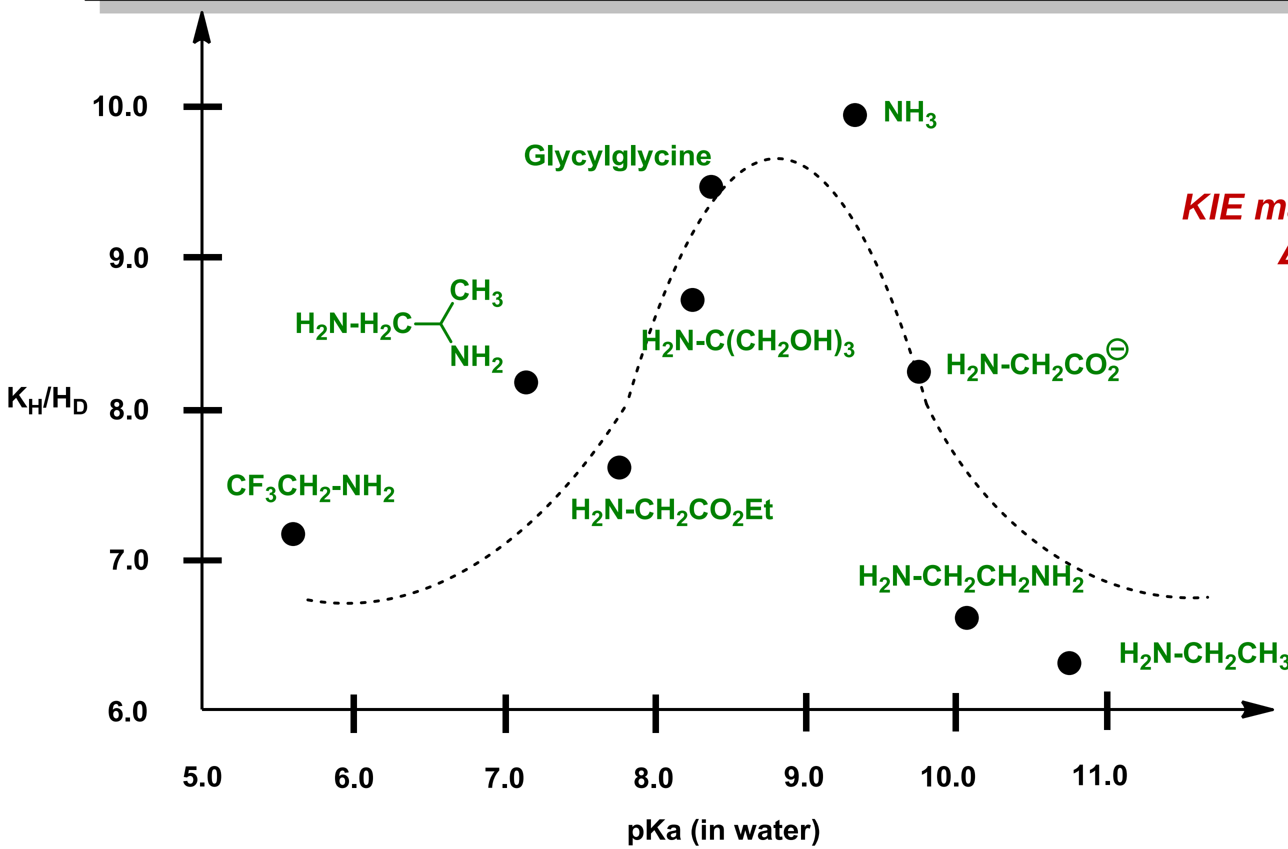
$$\Delta\Delta ZPE = \Delta ZPE_{C\text{-}H} - \Delta ZPE_{C\text{-}D}$$

Maximal KIE with symmetrical T.S.

F. H. Whestheimer, *Chem. Rev.*, **1961**, *61*, 295 - G. H. Hammond , *JACS*, **1955**, *77*, 334

Kinetic Isotope Effects Onto Acidity





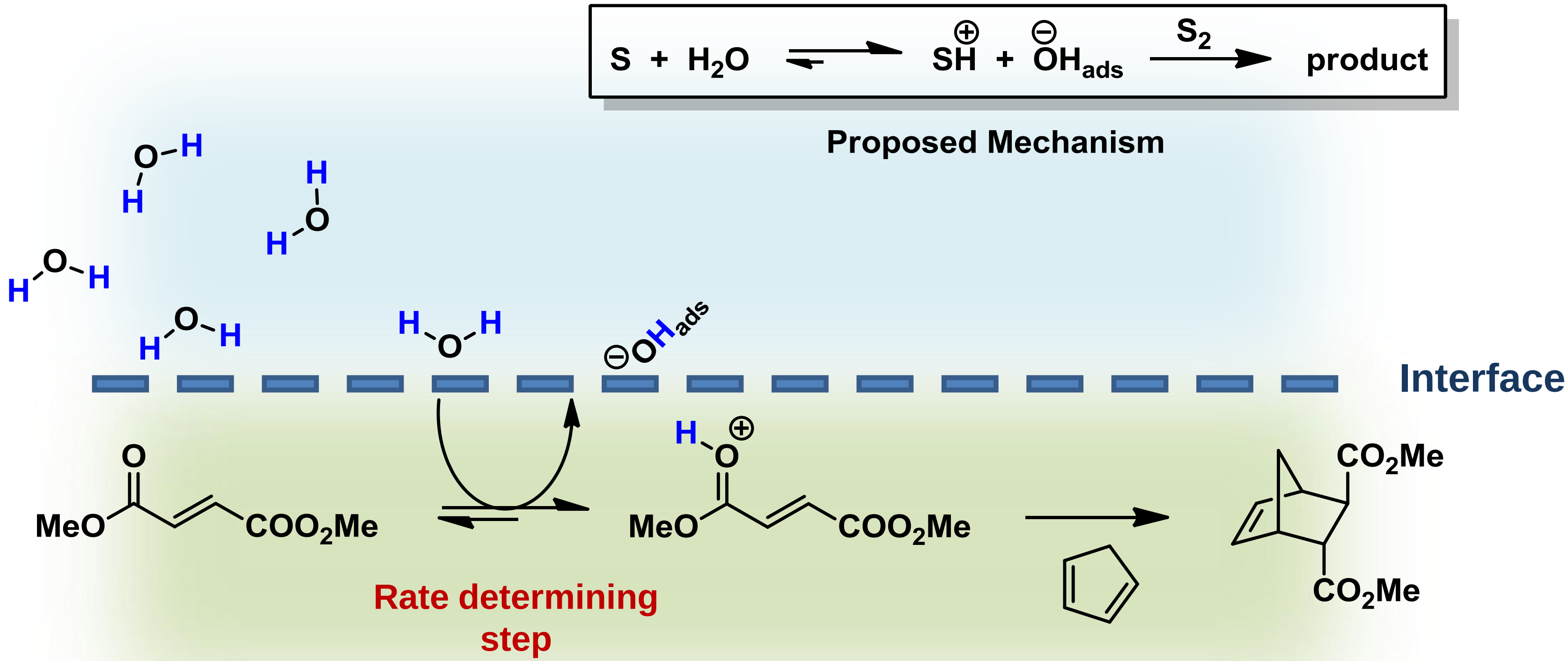
KIE maximum when ΔpKa ~ 0

J. E. Dixon, T. C. Bruice, *JACS*, **1969**, *92*, 905

Solvent Kinetic Isotope Effects

« On-water » chemistry :

- ✓ Reaction mixture must be heteregeneous
- ✓ Interface must be with aquous phase
- ✓ Reaction catalyzed on-water also catalyzed by H+
- ✓ Solvent isotope effect – Slower rate with D_2O

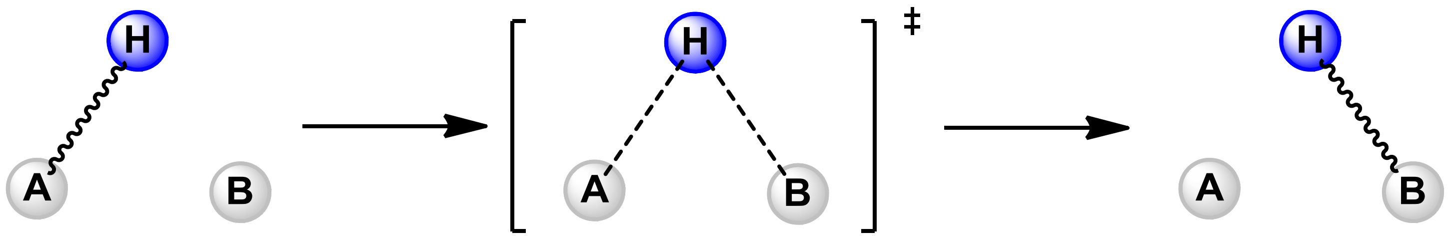


Up to twice faster than in THF or DCM

KIE = 1.4 with D_2O

J. K. Beattie, C. S. P. McEarlen, C. B. W. Phippen, *Chem. Eur. J.*, **2010**, *16*, 8972

Non-linear Transition States

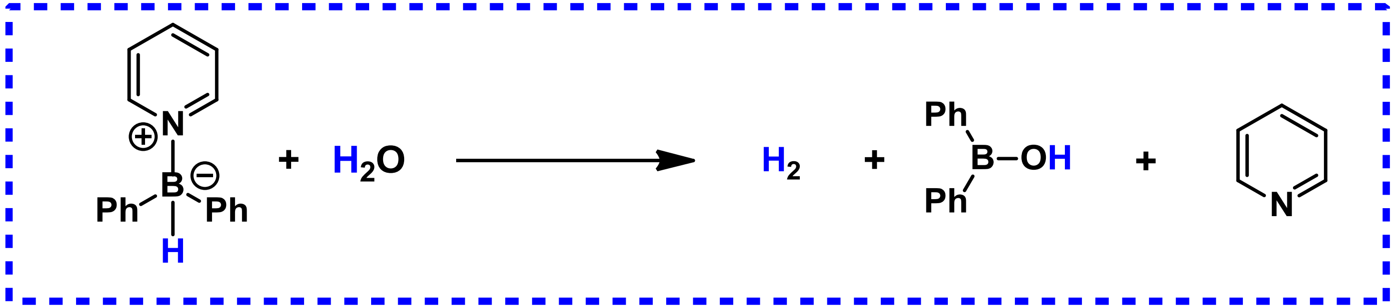


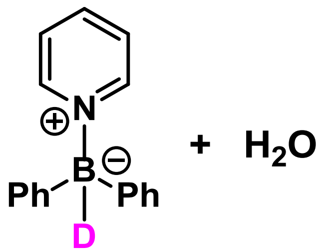
Non-linear symmetric transition state

Major distortion of the bond going to The T.S.

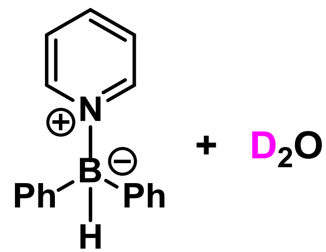
Bending vibrational are energitacally lower than stretching vibrational modes → KIE less important ~ 1.5 to 4.5

Non-linear Transition States

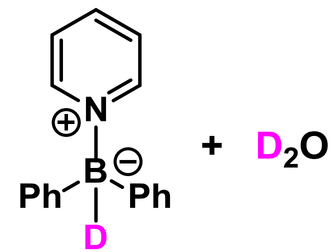




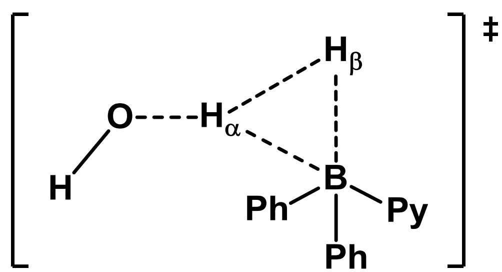
KIE = 1.54



KIE = 6.90



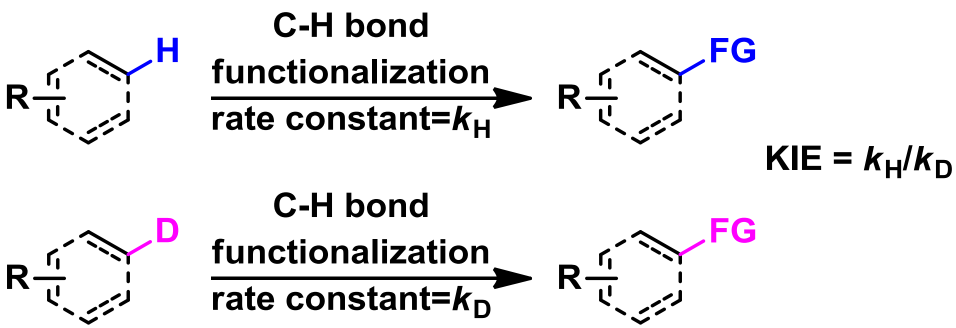
KIE = 10.3



T. S. proposed

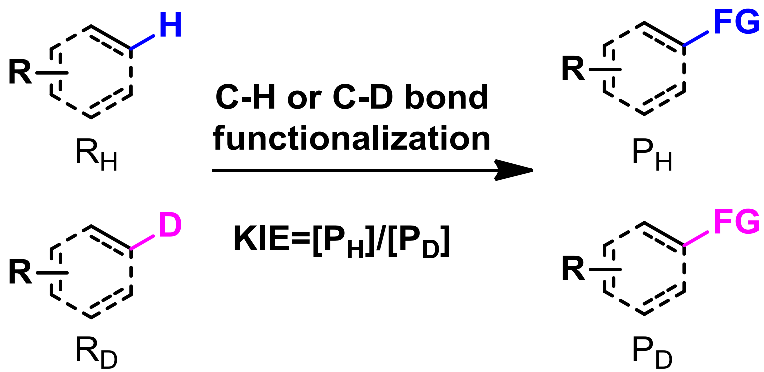
M. F. Hawthorne, E. S. Lewis, *JACS*, **1958**, *80*, 4296

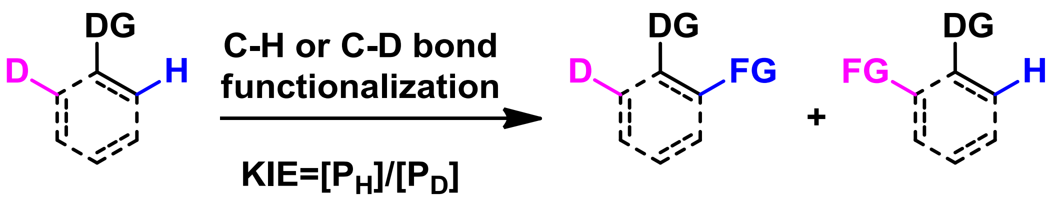
PKIE in Catalyzed C-H Bond Functionalizations



« Rate Determining Step »

« Product Determining Step »

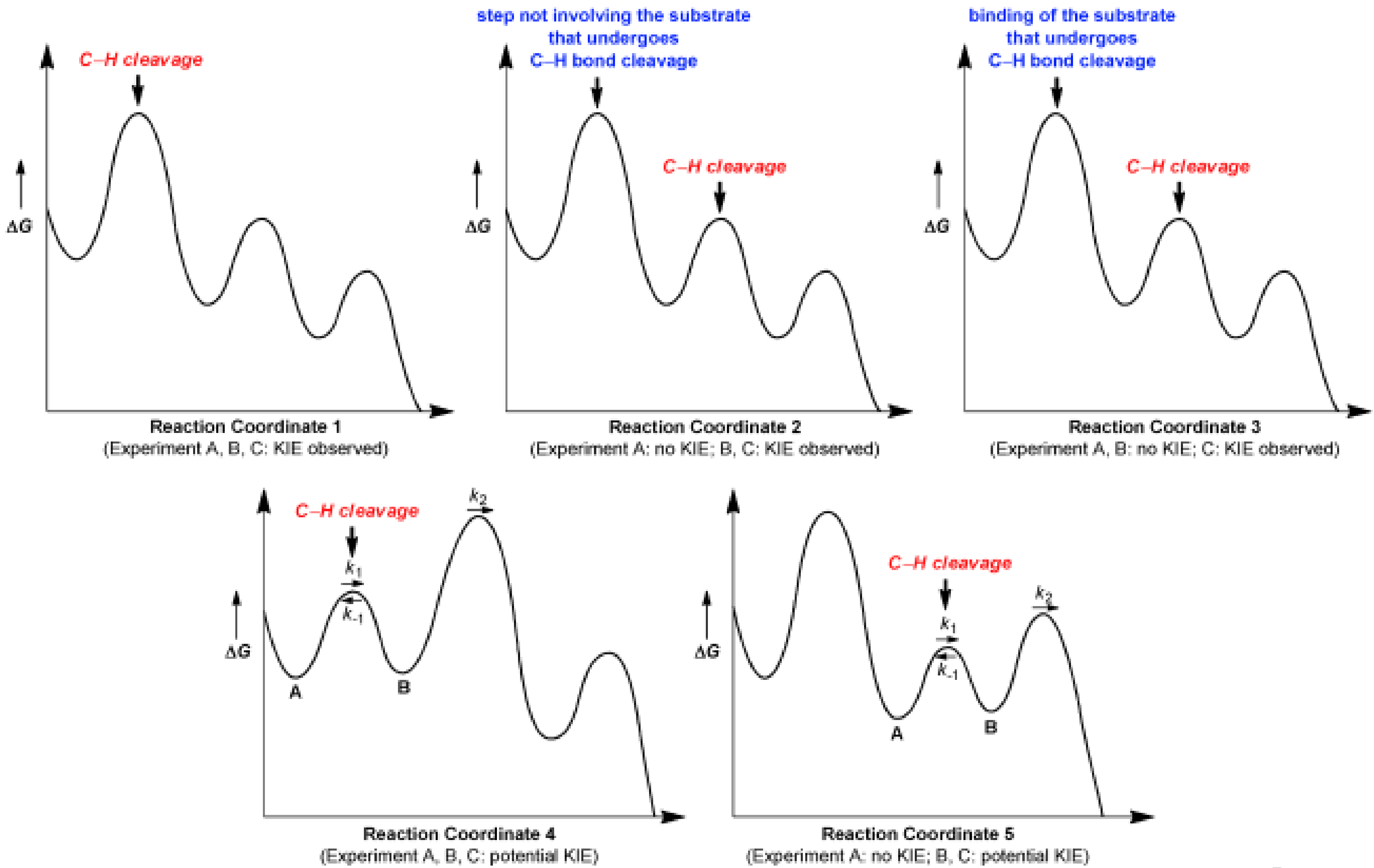




« Product Determining Step »

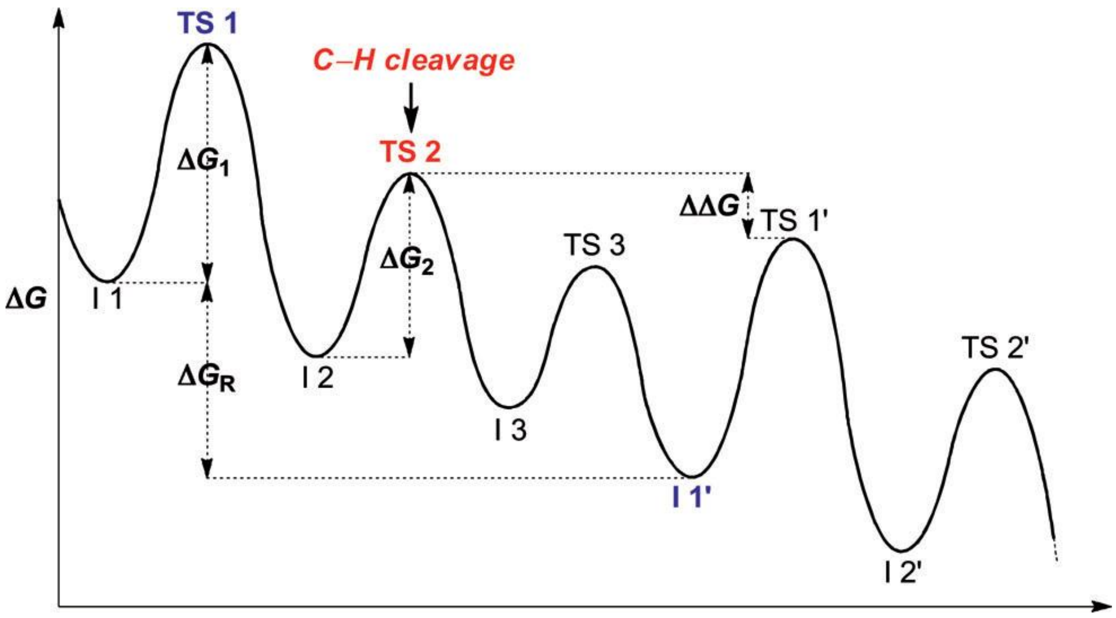
E. M Simmons, J. F. Hartwig, *ACIE*, **2012**, *51*, 3066

PKIE in Catalyzed C-H Bond Functionalizations



E. M Simmons, J. F. Hartwig, *ACIE*, **2012**, *51*, 3066

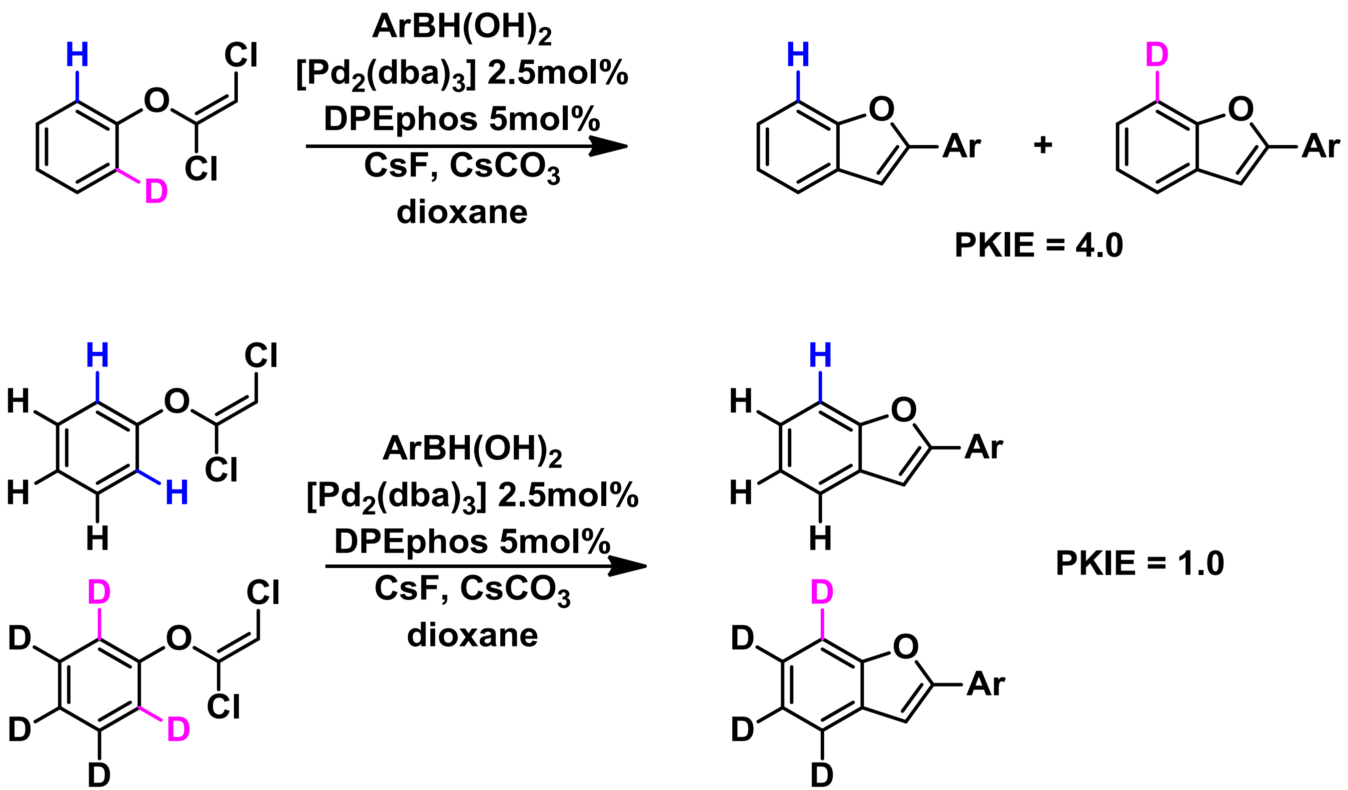
PKIE in Catalyzed C-H Bond Functionalizations



Complexity in catalytic reaction

E. M Simmons, J. F. Hartwig, *ACIE*, **2012**, *51*, 3066

PKIE in Catalyzed C-H Bond Functionalizations



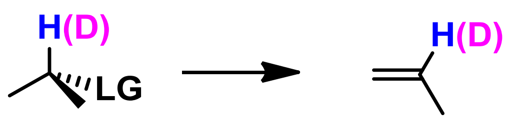
C-H bond cleavage not occures during the « turn-over determining step » but is the product determining step – In fact TDS is the oxidative addition of the C-Cl bond

L. M. Geary, P. G. Hultin, *Eur. J. Org. Chem.*, **2010**, 5563

Secondary Kinetic Isotope Effects

Normal SKIE

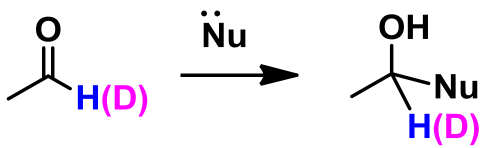
Hybridization changing onto α position
- Decreasing of p character
- $sp^3 \rightarrow sp^2 \rightarrow sp$



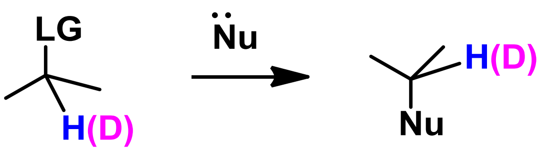
Hyperconjugation in β position

Inverse SKIE

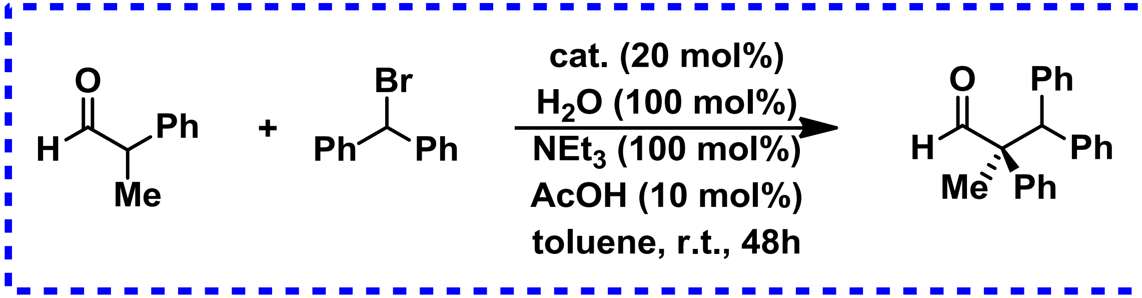
Hybridization changing onto α position
- Increasing of p character
- $sp \rightarrow sp^2 \rightarrow sp^3$

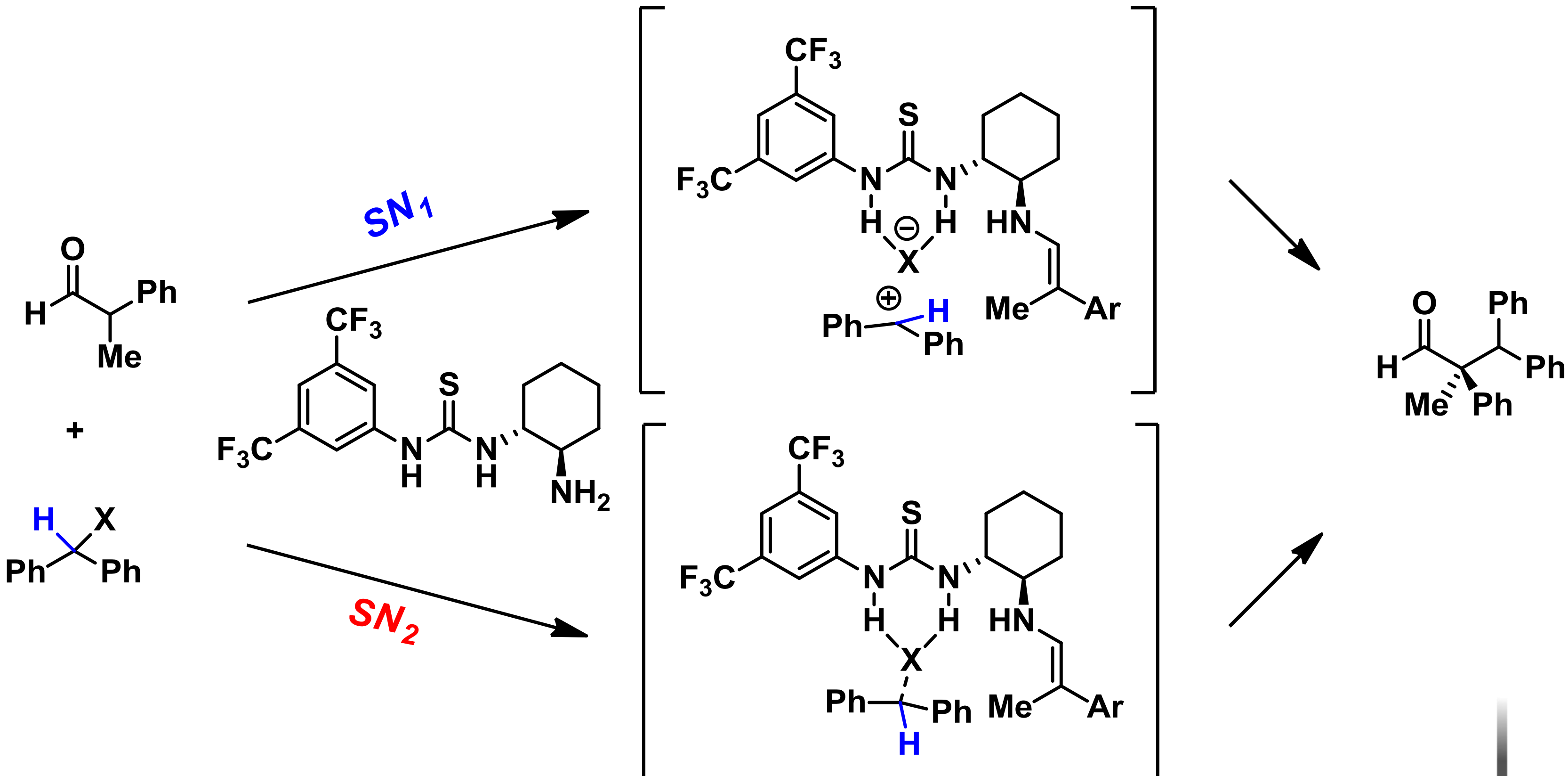


Steric effect in α, β, γ or other position



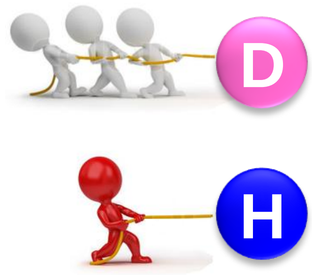
An Simple Example of Mechanism Determination

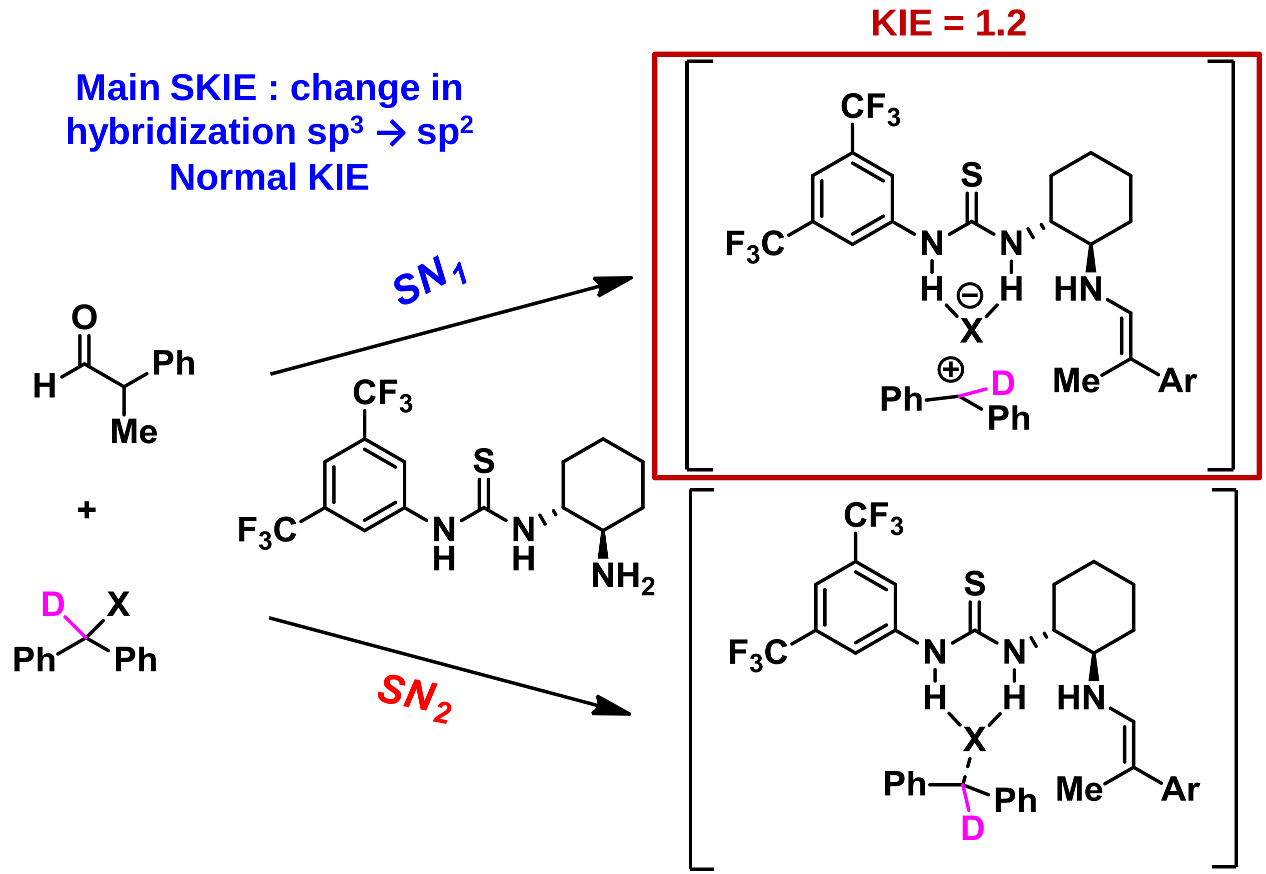




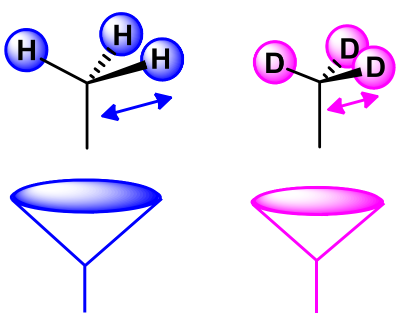
A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *JACS*, **2010**, *132*, 9286

An Simple Example of Mechanism Determination





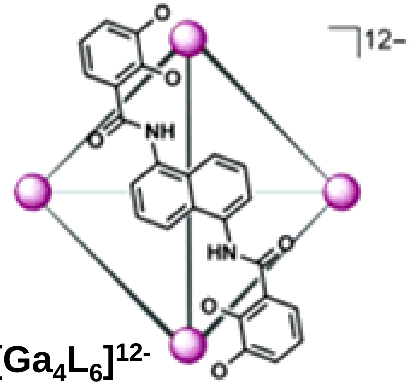
Main SKIE : steric effects
Inverse KIE



C-H bond is approximatively 0.005 A larger than C-D bond

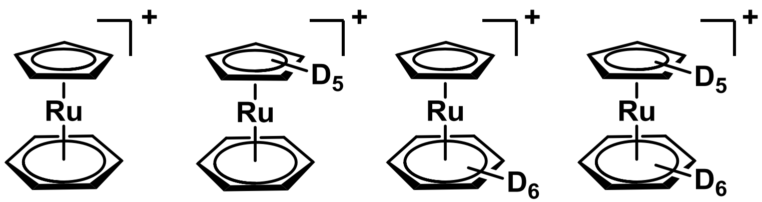
A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *JACS*, **2010**, *132*, 9286

Observed KIE Are the Sum of all the KIEs



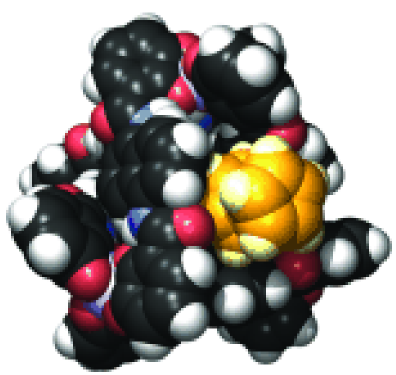
Host = $[Ga_4L_6]^{12-}$

Monocationic and neutral molecule encapsulation



[D_0] **[D_5]** **[D_6]** **[D_{11}]**

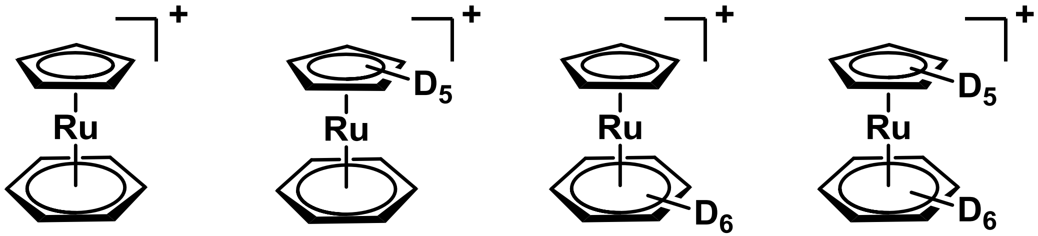
Guest = D_n[CpRu(η^6-benzene)]



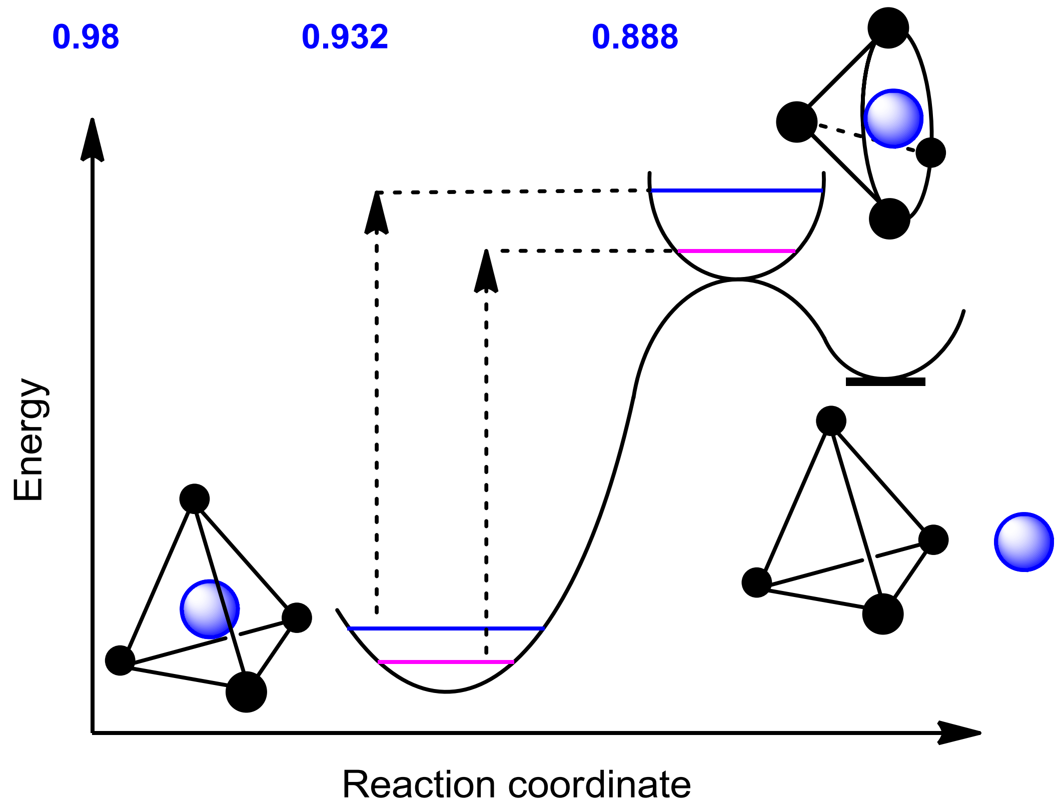
$\xrightleftharpoons{PEt_4^{\oplus}}$ **HOST-PEt_4 + Ru-complex**

J. S. Mugridge, R. S. Bergamn, K. N. Raymond, *ACIE*, **2010**, *49*, 3635

Observed KIE Are the Sum of all the KIEs



	$[D_0]$	$[D_5]$	$[D_6]$	$[D_{11}]$
KIE	**1.0**	**0.98**	**0.932**	**0.888**



Bending
+
Steric
KIE

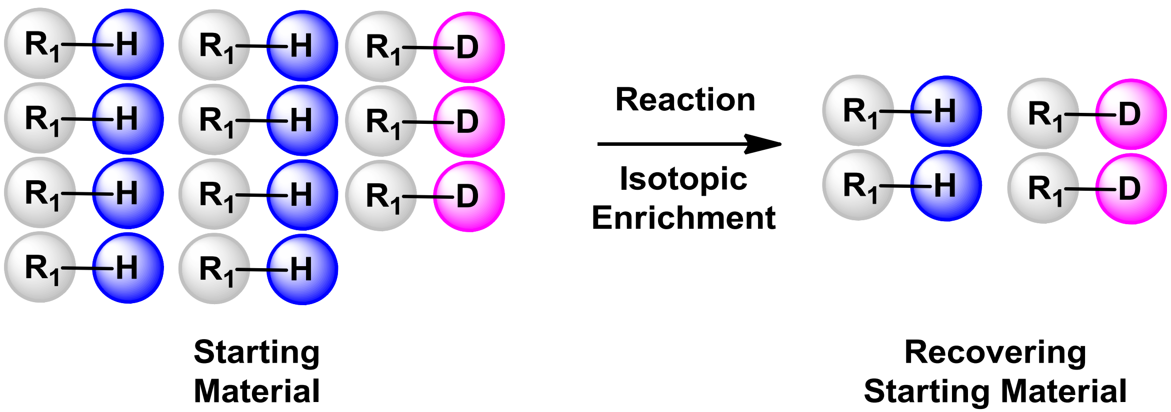
J. S. Mugridge, R. S. Bergamn, K. N. Raymond, *ACIE*, **2010**, *49*, 3635

The Singleton Method

The Singleton Method

Drawbacks of the previous methods :
- **precision in absolute rate measurements**
- **difficulties for observation of small KIE**
- **arduous synthesis of isotopically labeled material**

A great idea : « *as any reaction proceeds, the starting materials are fractionatively enriched in isotopically slower-reacting components* »

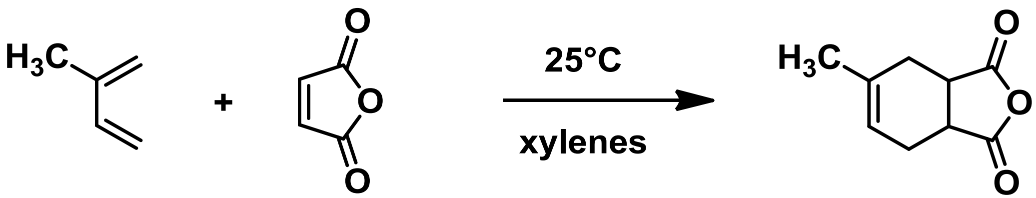


$$R/R_0 = (1 - F)^{(1/KIE)-1}$$

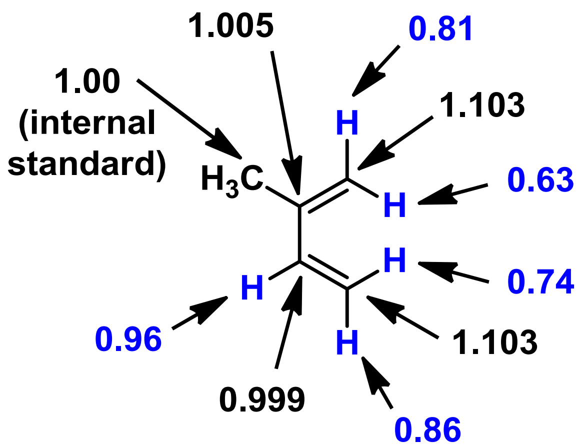
R/R₀, the proportion of a minor isotopic component in recovered material compared to the original starting material,
F, the fractional convertion of reactants
KIE, relative rate for the major/minor isotopic components

A. A. Thomas, D. A. Singleton, *JACS*, **1995**, *117*, 9357

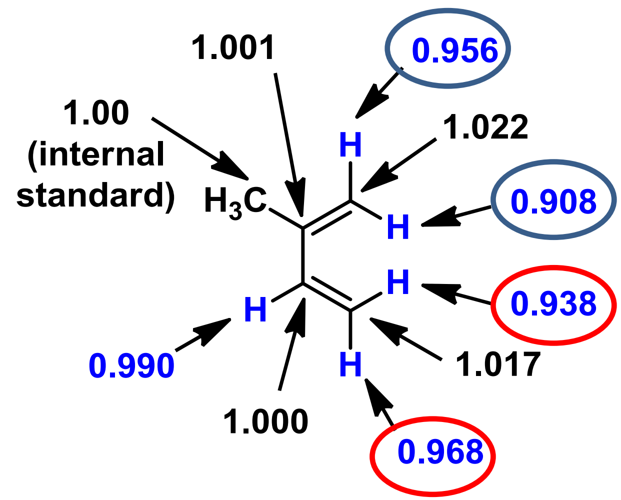
The Singleton Method



$$R/R_0 = (1 - F)^{(1/\mathrm{KIE})-1}$$



^{2}H and ^{13}C isotopic composition of isoprene recovered from a reaction to 98.9% completion

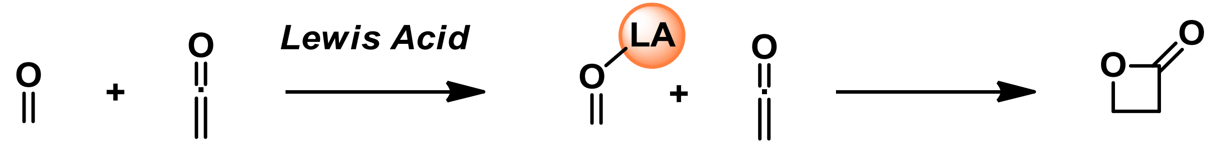


^{2}H and ^{13}C calculated from the equation above

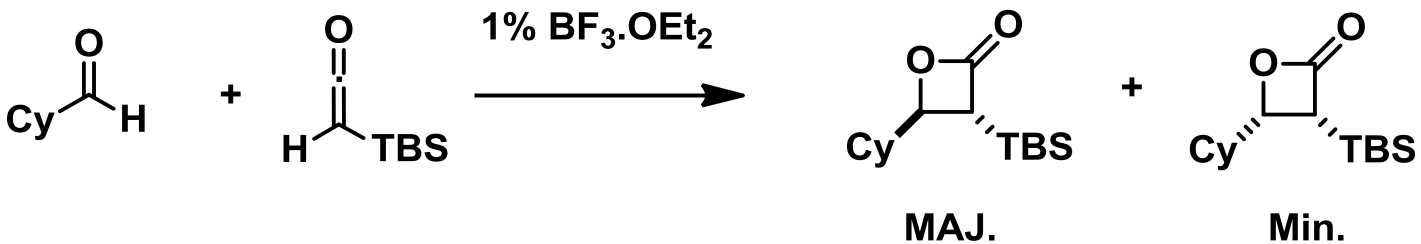
Quick obtention of highly detailed KIE informations employing routine instruments

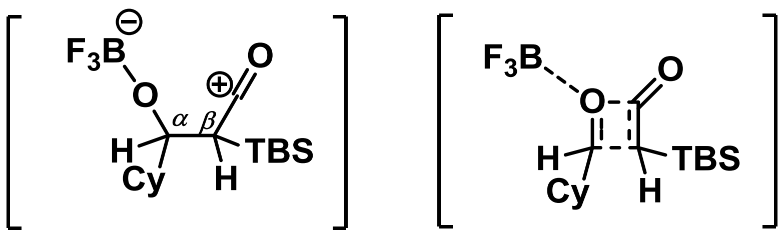
A. A. Thomas, D. A. Singleton, *JACS*, **1995**, *117*, 9357

The Singleton Method – Mechanistic Studies



Experimental observations :



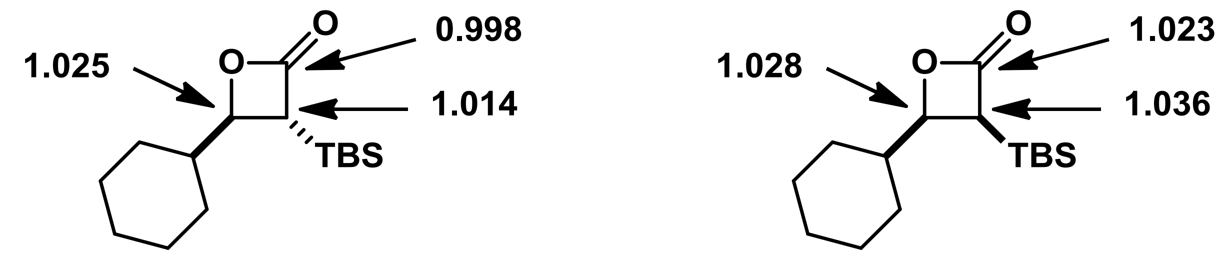


Concerted or Stepwise mechanism ?

What is the origin of the selectivity ?

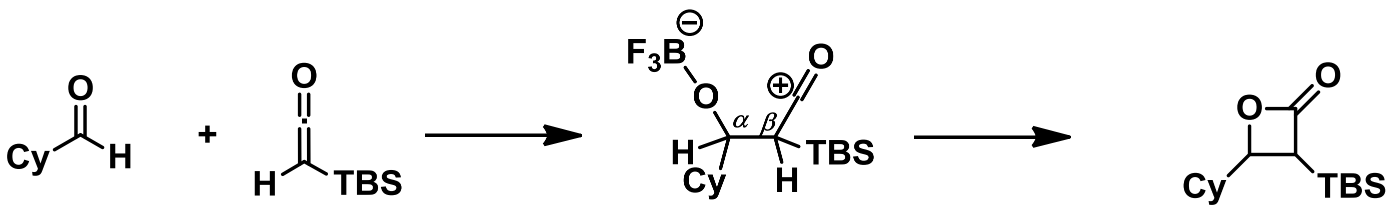
D. A. Singleton, Y. Wang, H. W. Yang, D. Romo, *ACIE*, **2002**, *41*, 1572

The Singleton Method – Mechanistic Studies



^{13}C KIE at natural abundance

Stepwise mechanism proposed with different limiting steps

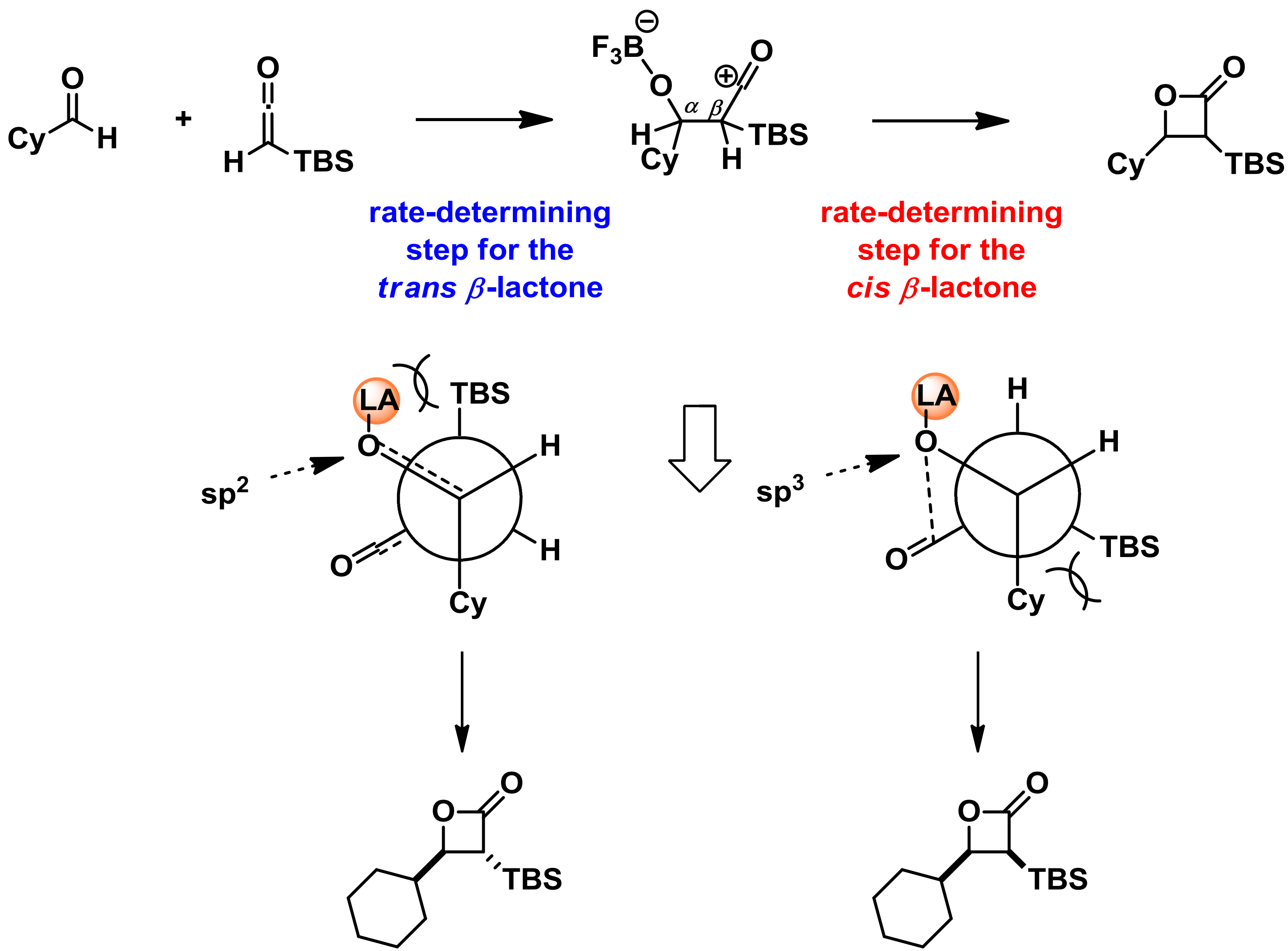


rate-determining step for the *trans* β-lactone

rate-determining step for the *cis* β-lactone

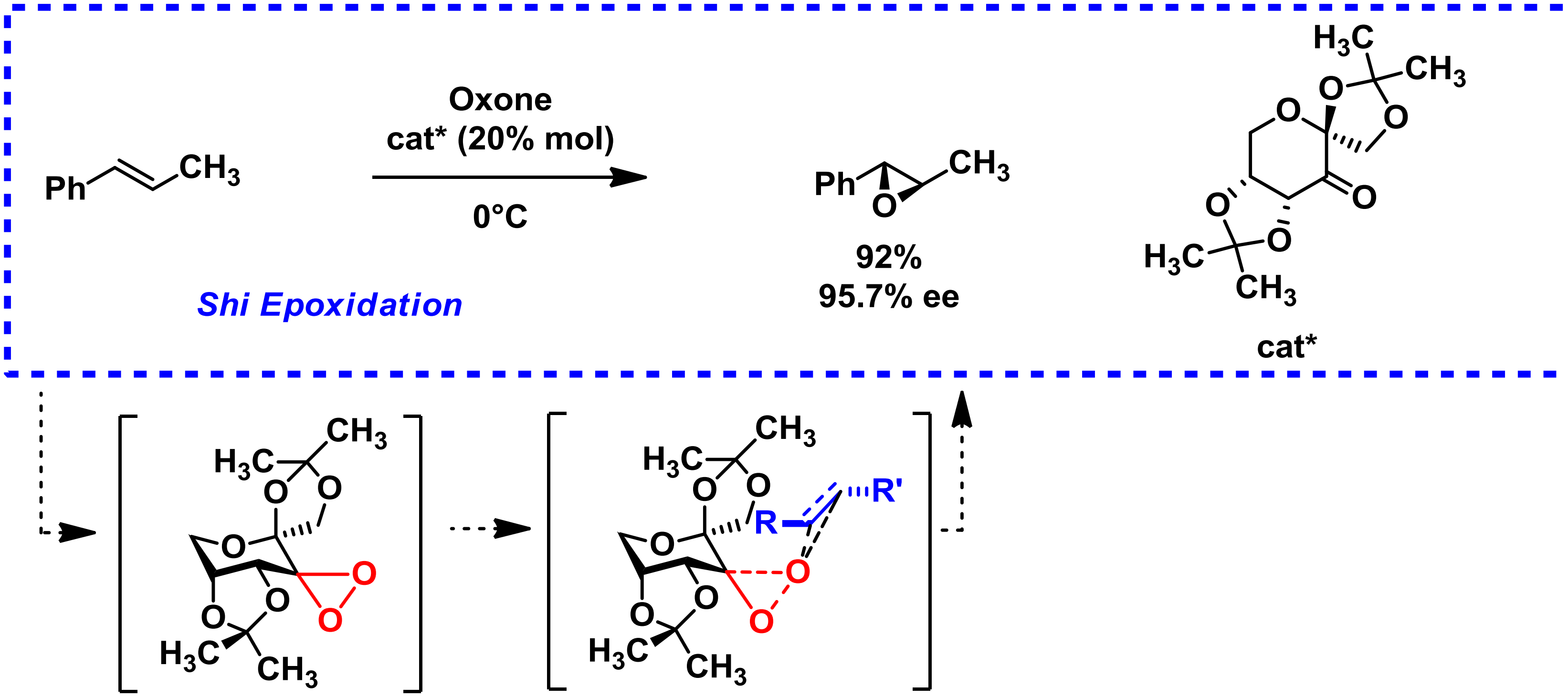
D. A. Singleton, Y. Wang, H. W. Yang, D. Romo, *ACIE*, **2002**, *41*, 1572

The Singleton Method – Mechanistic Studies

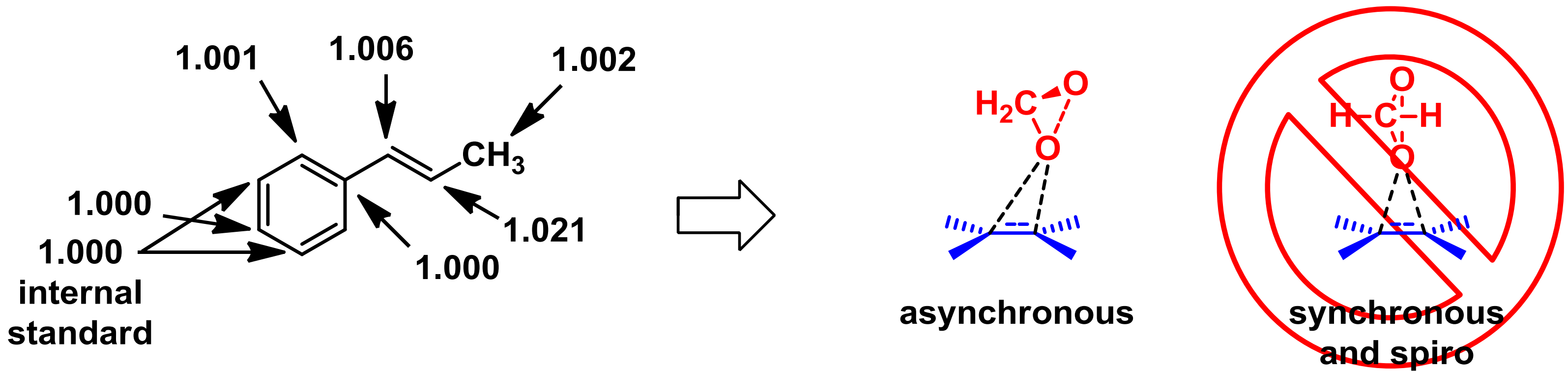


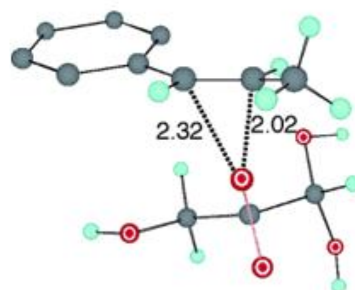
D. A. Singleton, Y. Wang, H. W. Yang, D. Romo, *ACIE*, **2002**, *41*, 1572

The Singleton Method – Mechanistic Studies



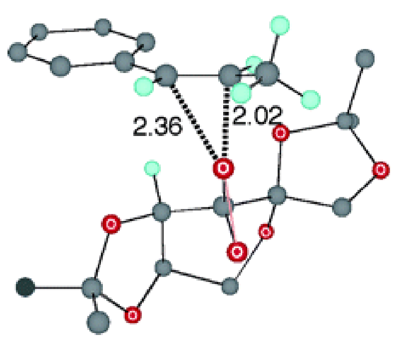
The Singleton Method – Mechanistic Studies



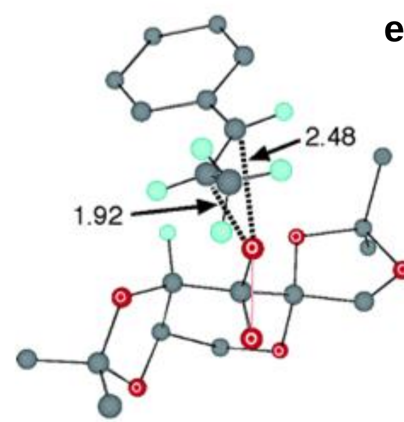


« Natural » asynchronicity
non-hindred catalyst

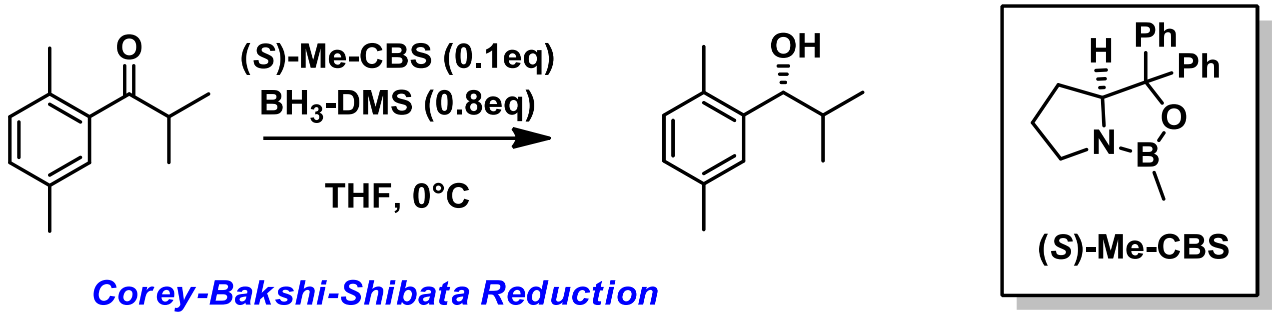
T.S. for the favor
enantiomer



T.S. for the disfavor
enantiomer



Deuteration of Enantiotopic Position



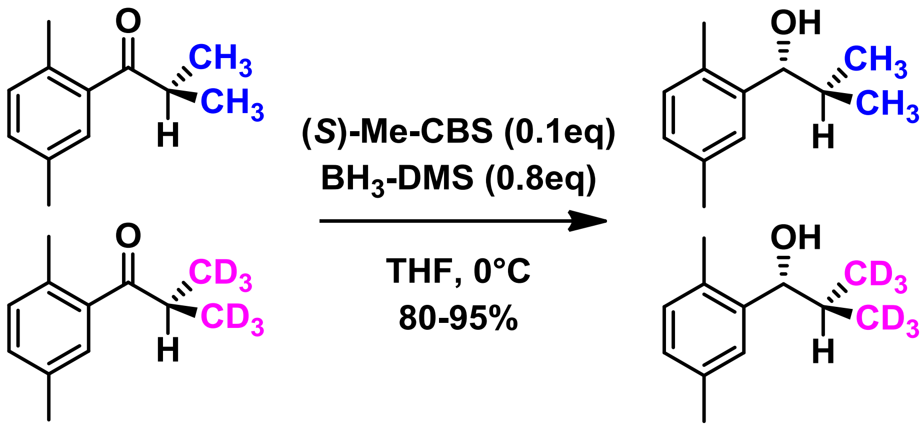
Corey-Bakshi-Shibata Reduction

Origin of Stereoselectivity ??

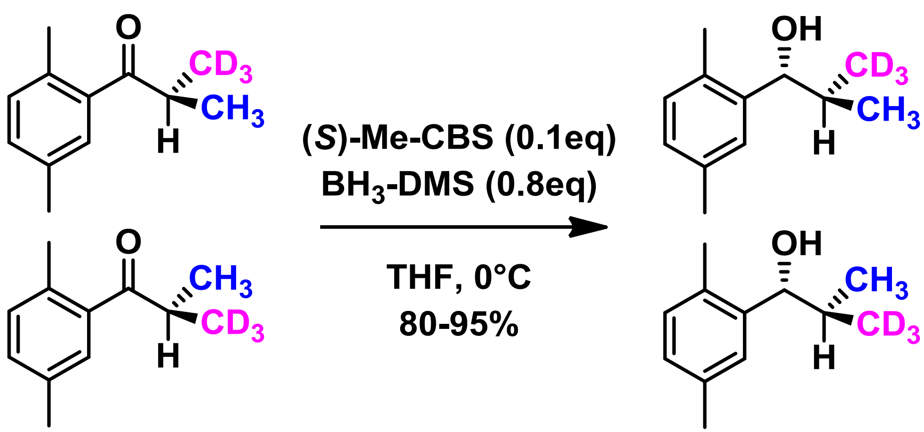
« In asymmetric reactions, the symmetry element
that makes these prochiral groups chemically equivalent is broken
in a deterministic way in the transition state »

M. P. Meyer, *Org. Lett.*, **2009**, *11*, 43338
- H. Zhu, D. J. O'Leary, M. P. Meyer, *ACIE*, **2012**, *124*, 12060

Deuteration of Enantiotopic Position



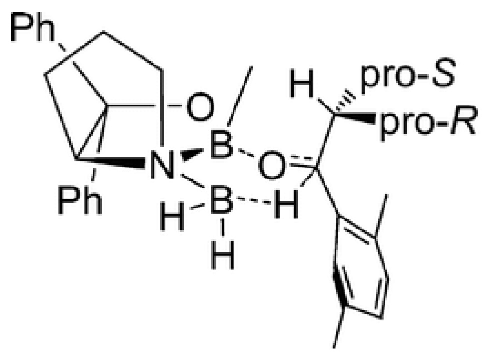
A **Measurement of the overall KIE resulting from ^{2}H-substitution upon the enantiotopic group**



B **Measurement of the ration of KIE resulting from each deuterated enantiotopic group**
- Unreacted starting material is reduced with (*S*)-Me-CBS

M. P. Meyer, *Org. Lett.*, **2009**, *11*, 43338
- H. Zhu, D. J. O'Leary, M. P. Meyer, *ACIE*, **2012**, *124*, 12060

Deuteration of Enantiotopic Position



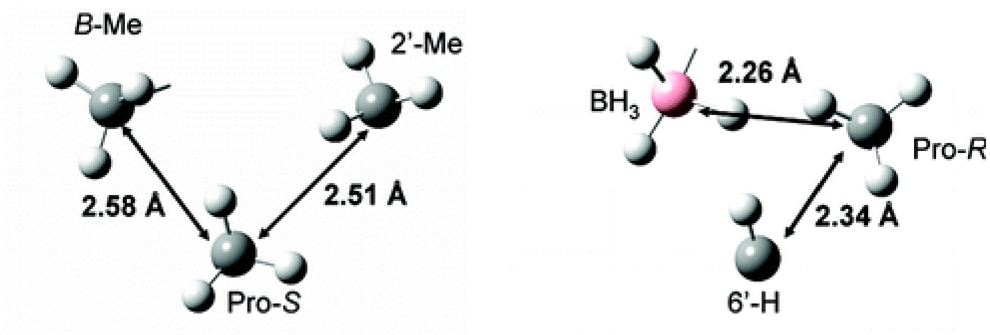
KIE$_{overall}$ = 0.939

KIE$_{pro\text{-}R\text{-}D3}$ = 0.965

KIE$_{pro\text{-}S\text{-}D3}$ = 0.974

Computed T.S. and KIE obtained

Boat-like T.S. favorised



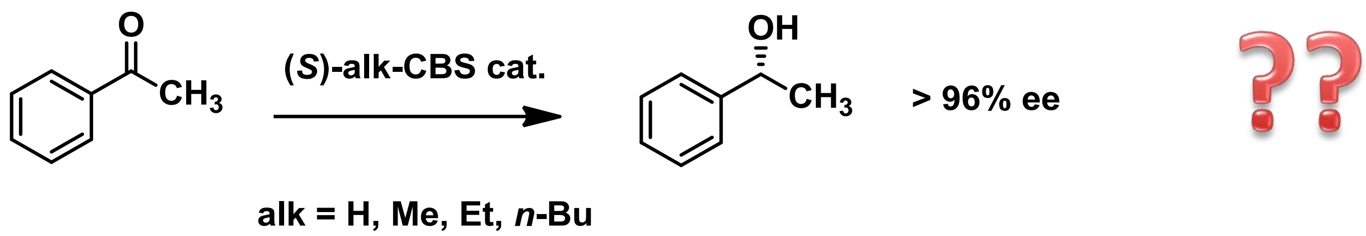
Computed calculations

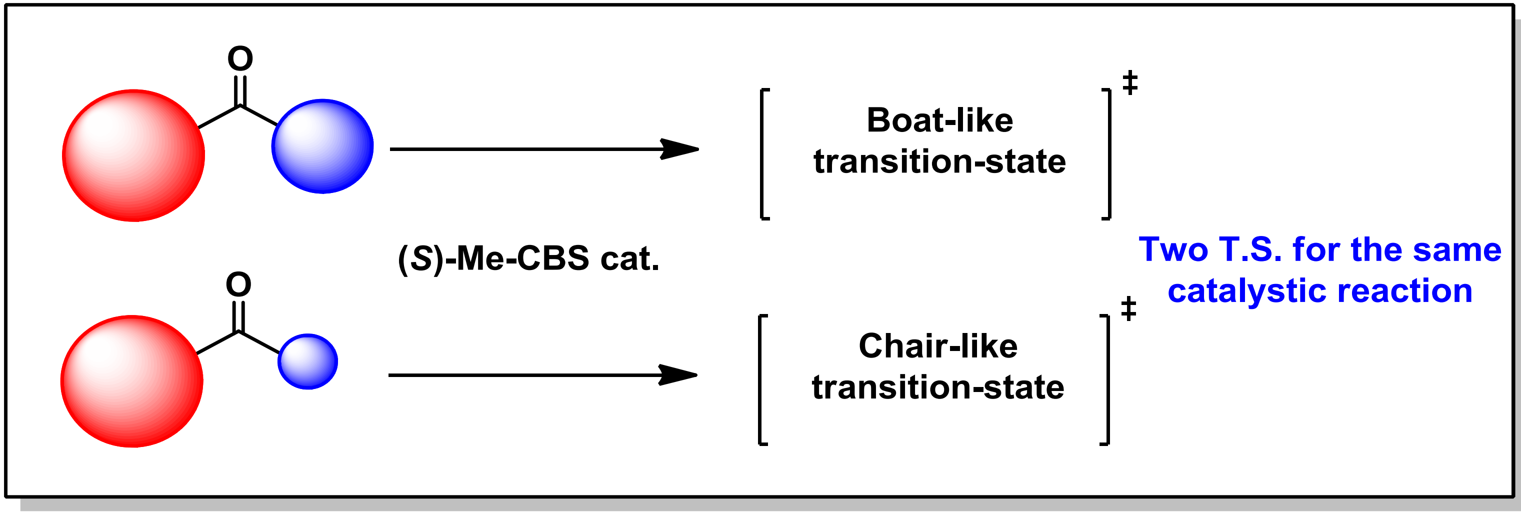
A single close proximity between CBS cat. and the prochiral substrate (*B*-Me and pro-S)

M. P. Meyer, *Org. Lett.*, **2009**, *11*, 43338
- H. Zhu, D. J. O'Leary, M. P. Meyer, *ACIE*, **2012**, *124*, 12060

The Singleton method

For acetophenone, enantioselectivity is not *B*-alkyl hindrance-dependant :





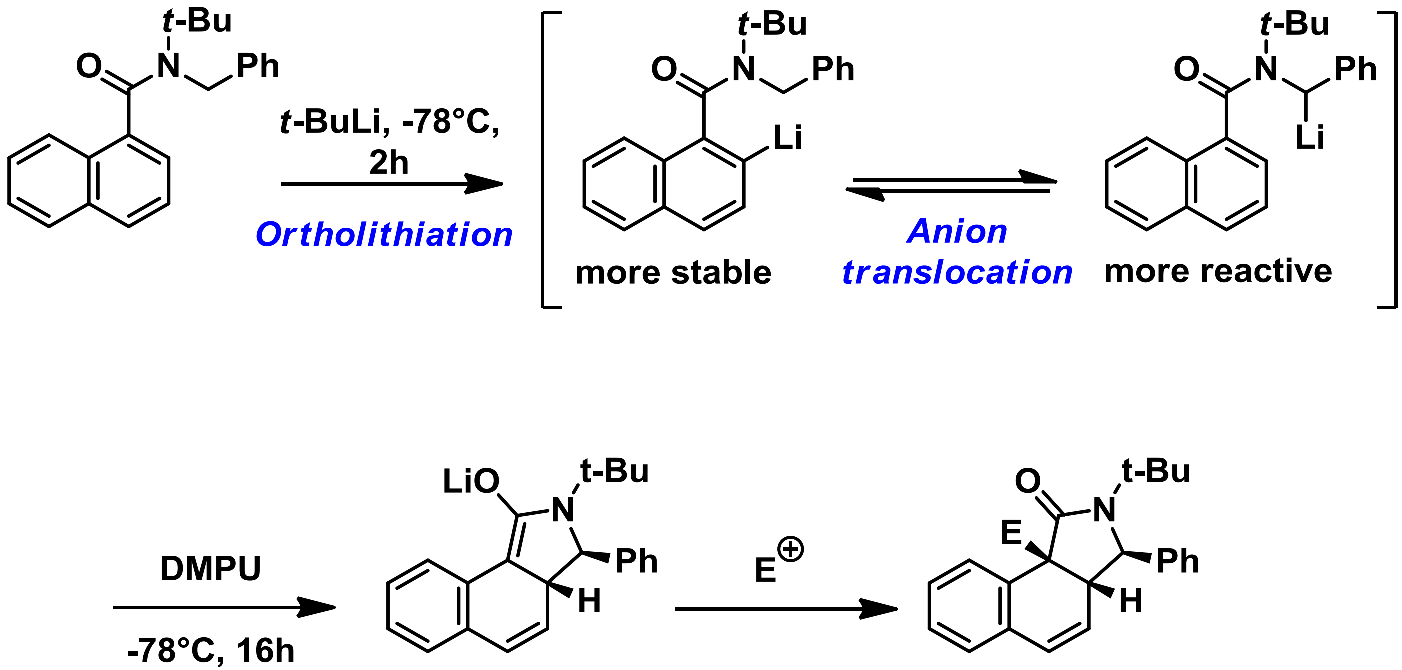
M. P. Meyer, *Org. Lett.*, **2009**, *11*, 43338
- H. Zhu, D. J. O'Leary, M. P. Meyer, *ACIE*, **2012**, *124*, 12060

Isotopes in Organic Synthesis :

An Efficient

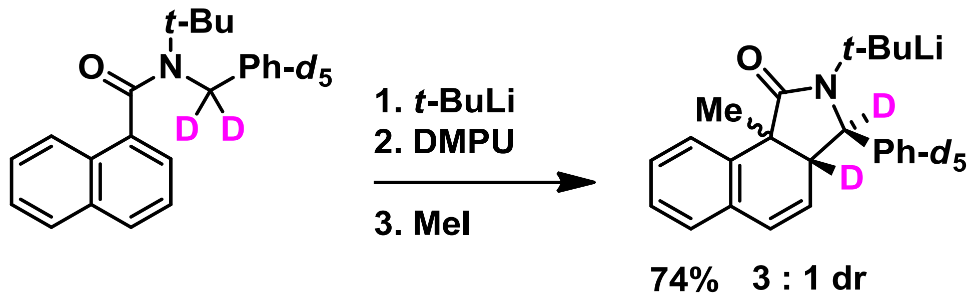
Directing and Protecting Group

Deuterium as Directing Group

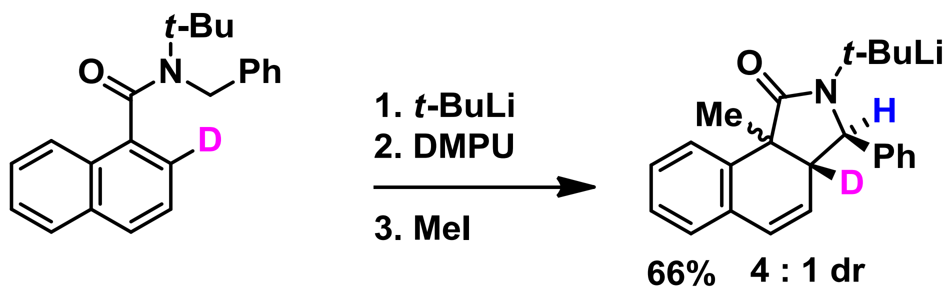


A. Ahmed, J. Clayden, M. Rowley, *Tetrahedron Lett.*, **1998**, *39*, 6103

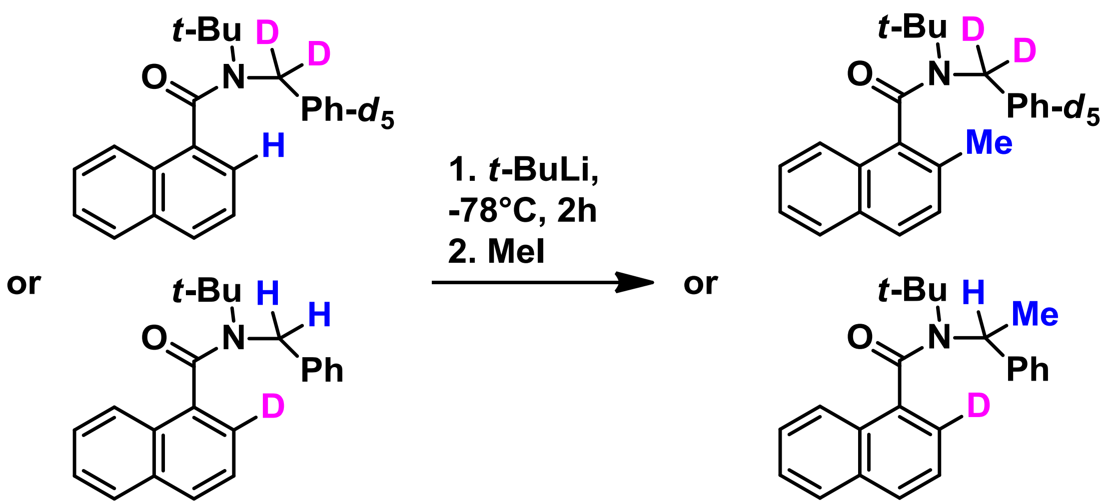
Deuterium as Directing Group



Proved *ortho*-lithiation followed by anion translocation



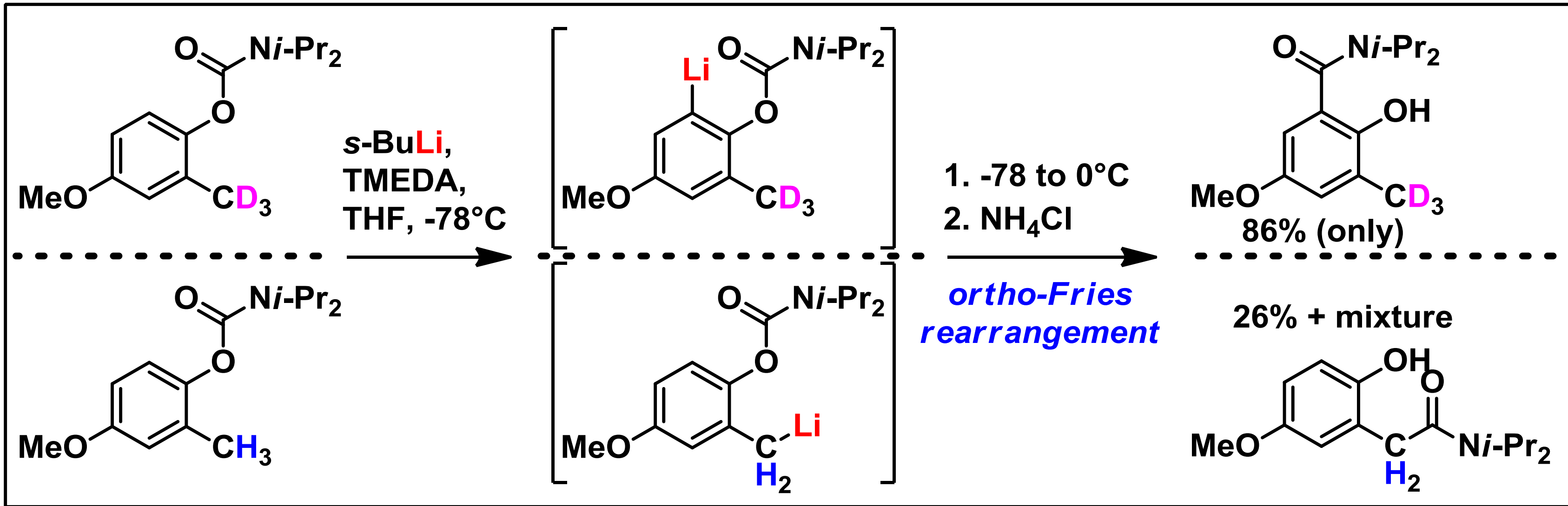
Direct lithiation in α position of nitrogen atom

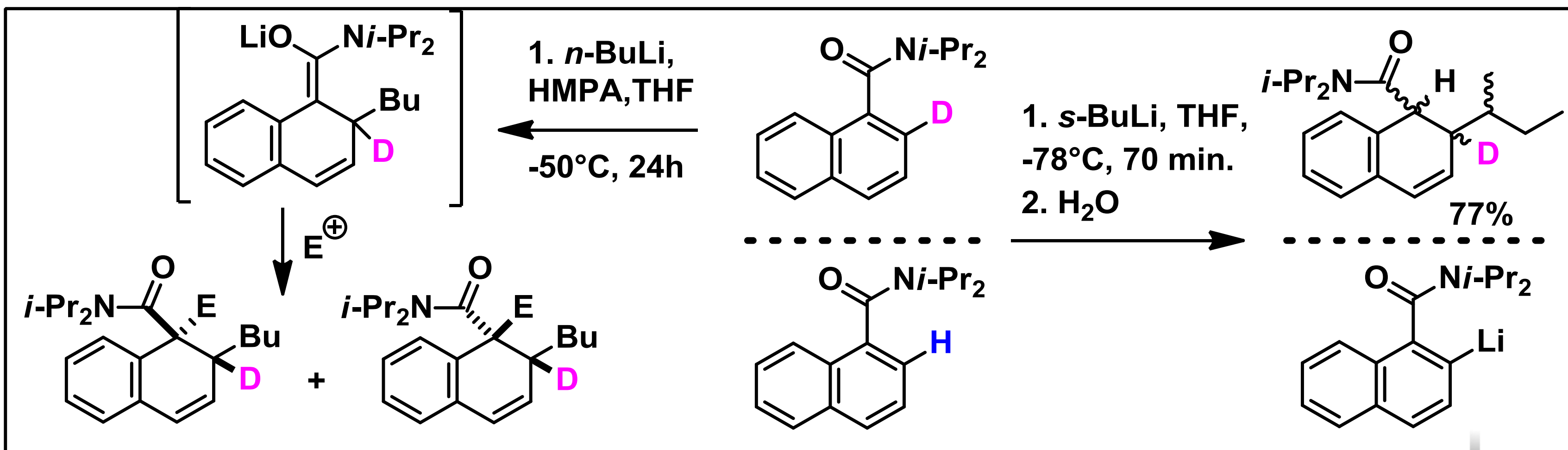


Deuterium as protecting group

A. Ahmed, J. Clayden, M. Rowley, *Tetrahedron Lett.*, **1998**, *39*, 6103

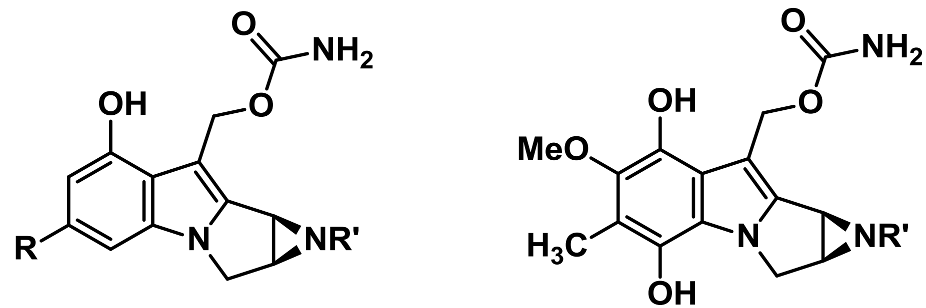
Deuterium as Directing Group



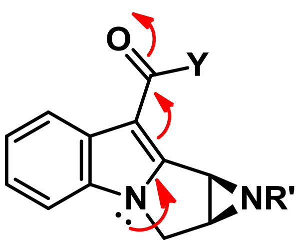


J. Clayden, J. H. Pink, N. Westlund, F. X. Wilson, *Tetrahedron Lett.*, **1998**, *39*, 8377

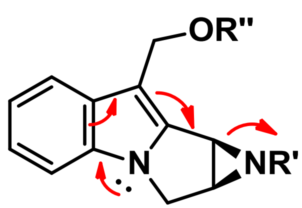
Deuterium as Protecting Group



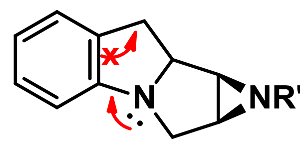
Leucoaziridinomitosenes



Stable tetracycle



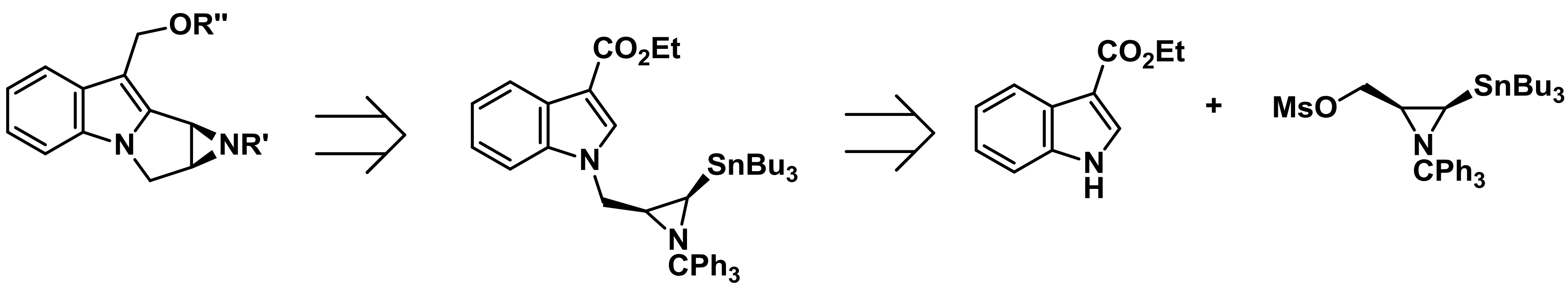
Unstable tetracycle

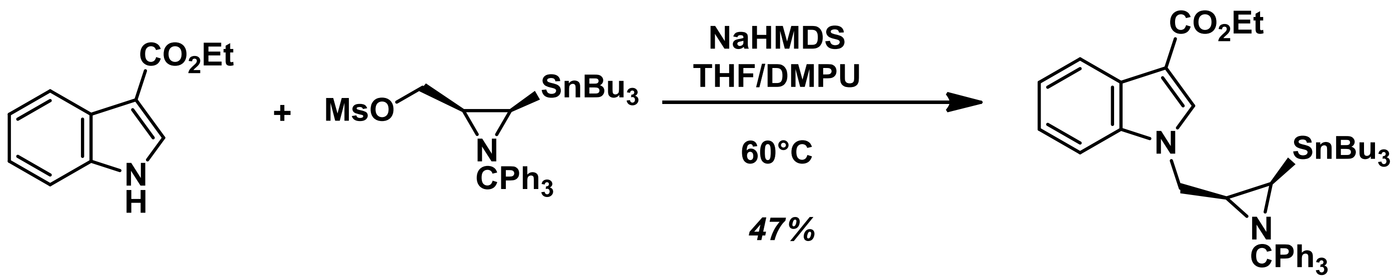


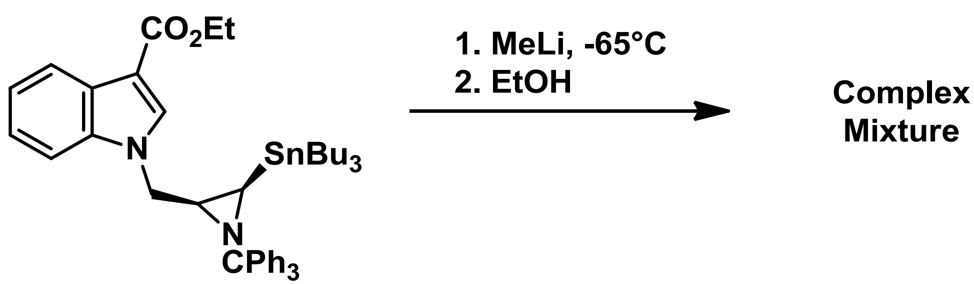
Stable tetracycle

E. Vedejs, J. Little, *JACS,* **2002**, *124*, 749

Deuterium as Protecting Group

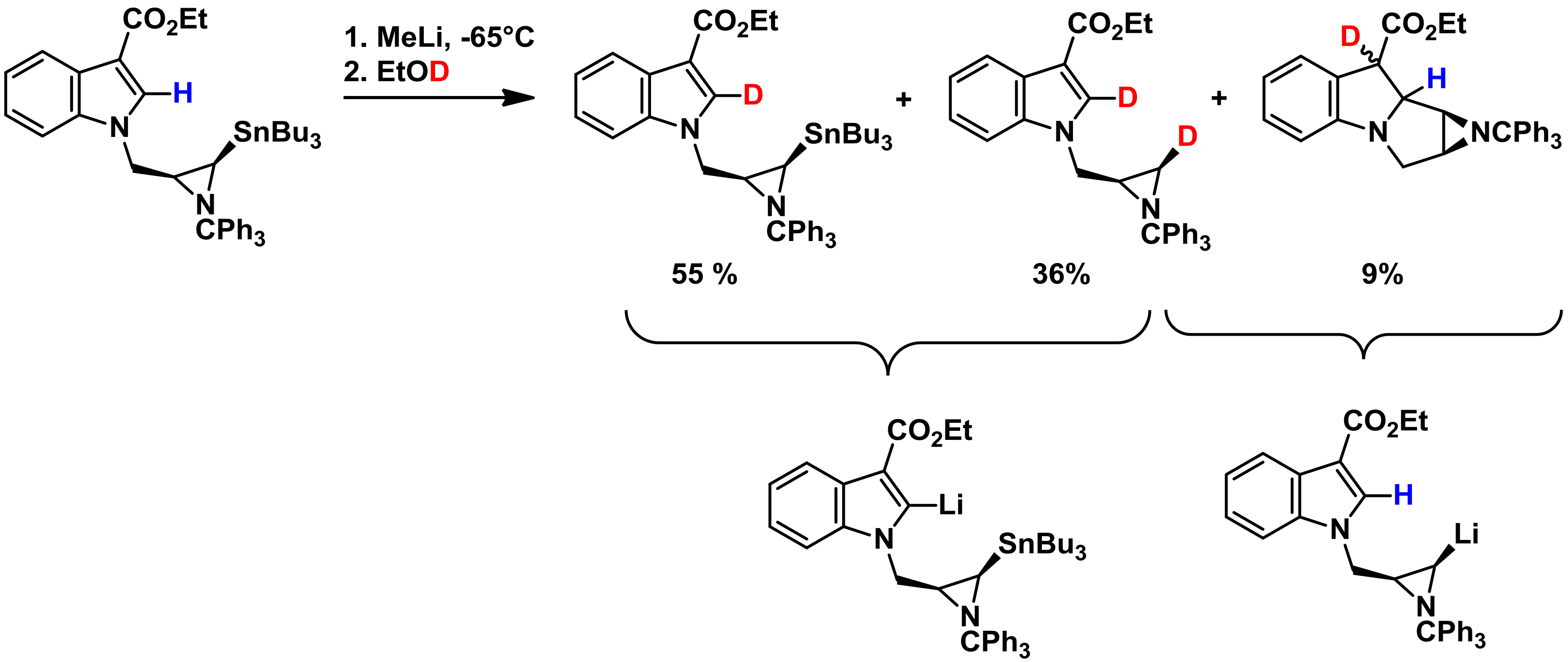






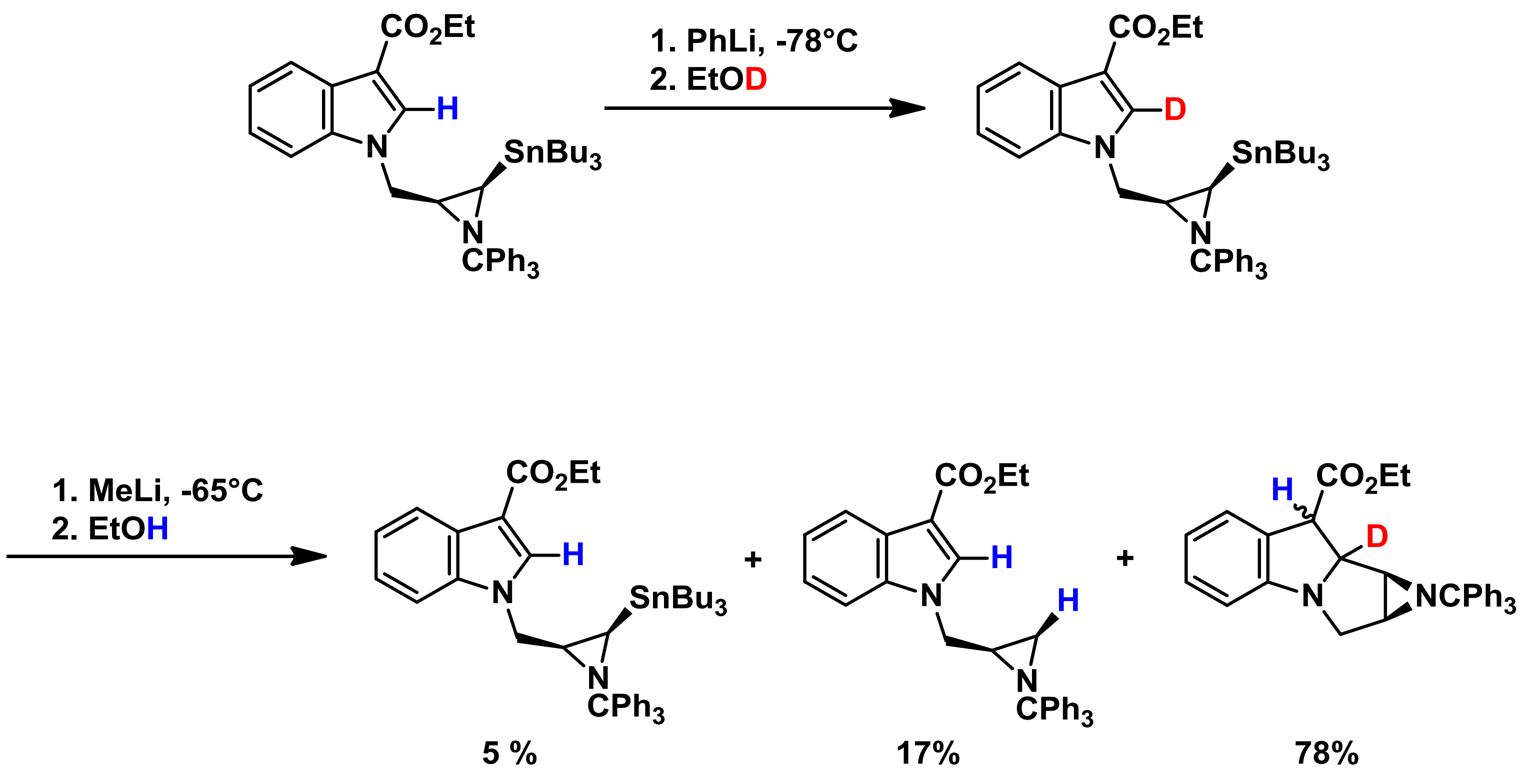
E. Vedejs, J. Little, *JACS*, **2002**, *124*, 749

Deuterium as Protecting Group



E. Vedejs, J. Little, *JACS,* **2002**, *124*, 749

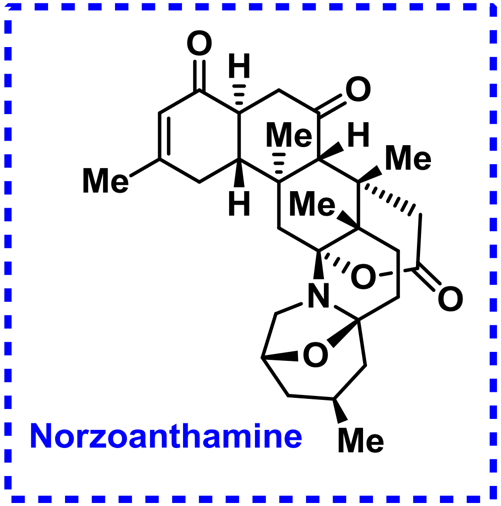
Deuterium as Protecting Group

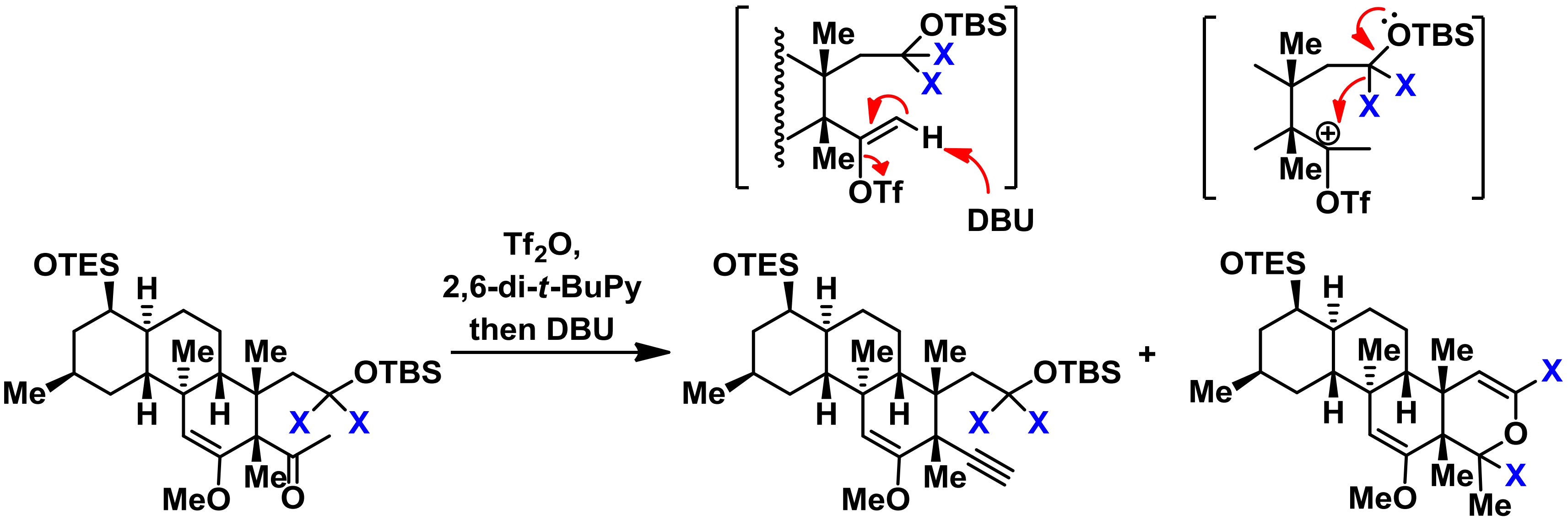


KIE ~ 35

E. Vedejs, J. Little, *JACS,* **2002**, *124*, 749

Deuterium as Protecting Group



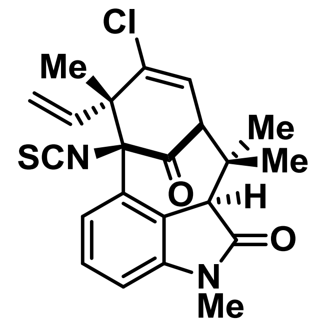


Desired alkyne
66% if X = H
81% if X = D

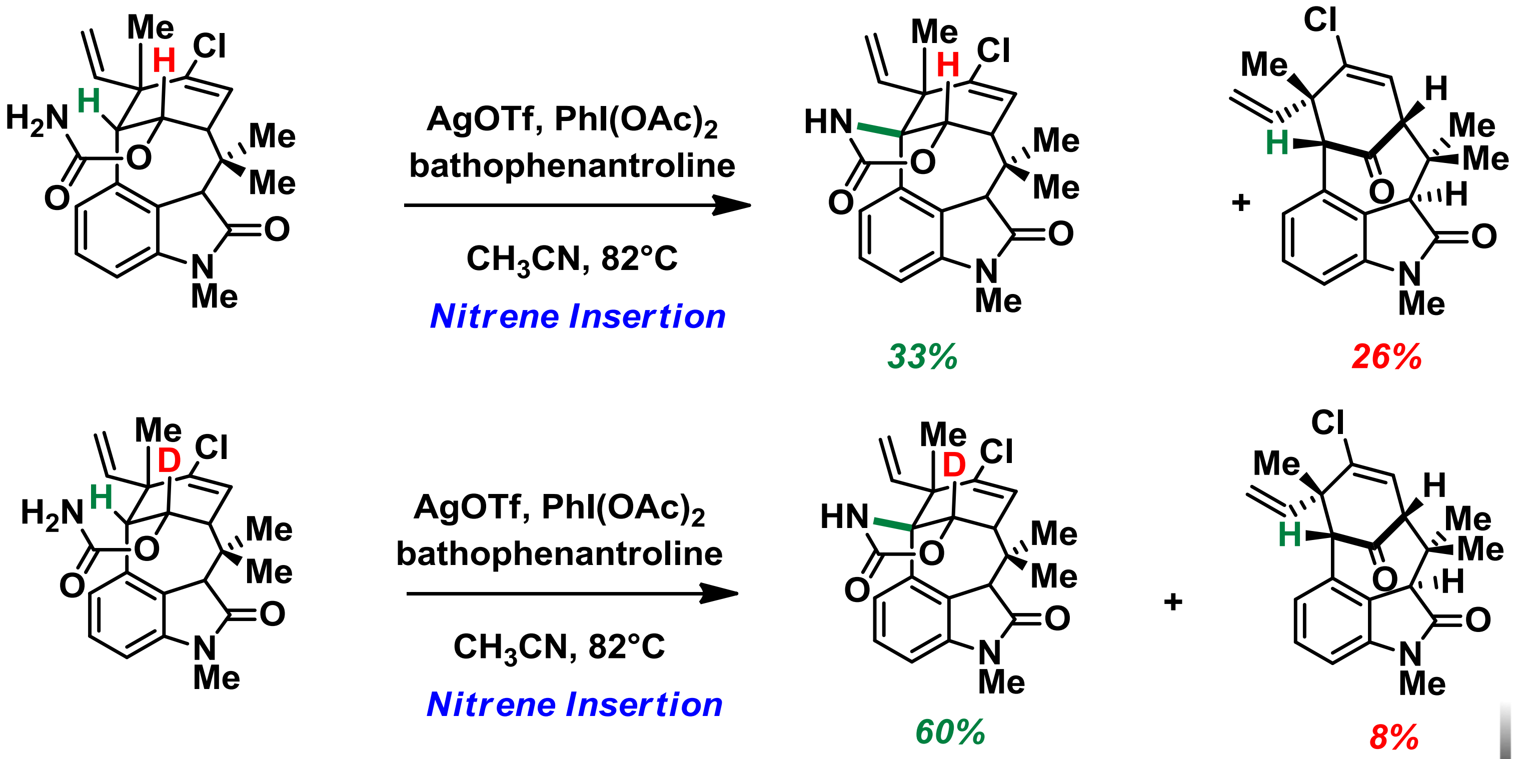
Byproduct
30% if X = H
9% if X = D

M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, K. Tanino, *Science*, **2004**, *305*, 495

Deuterium as Protecting Group



(-)-N-methylwelwitindoline C isothiocyanate



K. W. Quasdorf, A. D. Huters, M. W. Lodewyk, D. J. Tantillo, N. Garg, *JACS*, **2012**, *134*, 1396

Conclusion

- **Useful tool for mechanism determination**
- **Very simple studies with the Singleton method**
- **An efficient protecting group for carbon atom**

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F. H. Westheimer, *Chem. Rev.*, **1961**, *61*, 295

M. Gomez-Gallego, M. A. Sierra, *Chem. Rev.*, **2011**, *111*, 4857

J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *ACIE*, **2007**, *46*, 7744

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R. Knowles - *Mac Millan group meeting*, **sept. 2005**, Kinetic Isotope Effects in Organic Synthesis