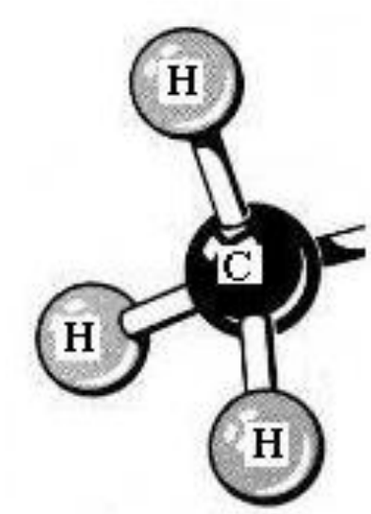
# *Demystifying the Magic Methyl Effect*




**methyl group**

Patricia Zhang
MacMillan Group Meeting
June 11, 2015

# *Demystifying the Magic Methyl Effect*

Angewandte Reviews

T. Cernak and H. Schönherr

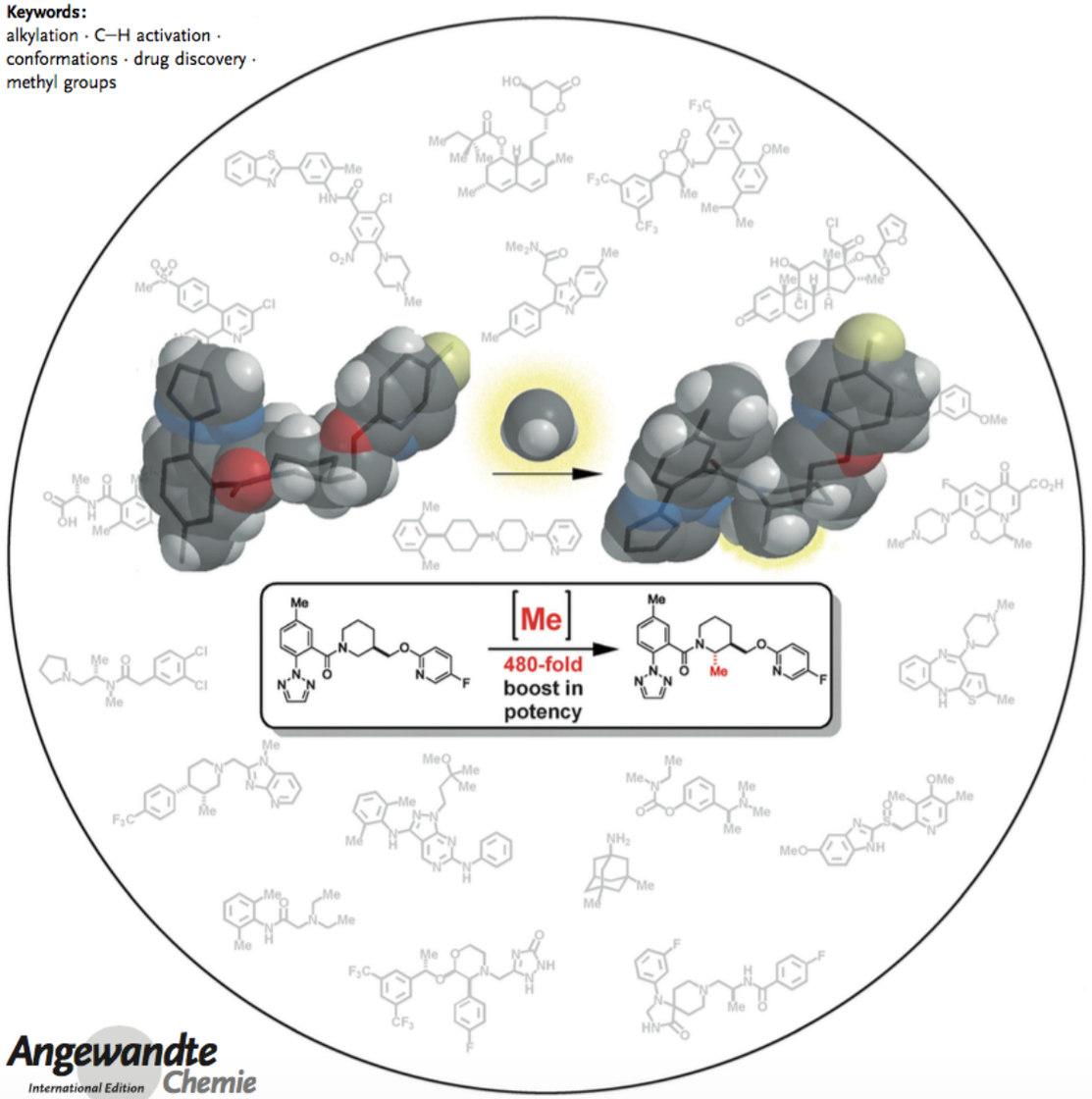
DOI: 10.1002/anie.201303207

Methylation

## Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions

*Heike Schönherr and Tim Cernak**

**Keywords:**
alkylation · C–H activation · conformations · drug discovery · methyl groups



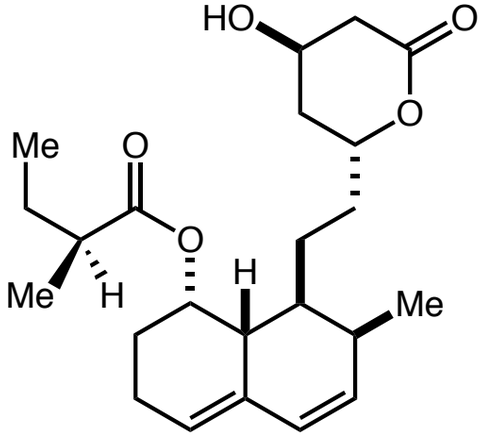
# *Demystifying the Magic Methyl Effect*

## When is the Magic Methyl Effect in play?

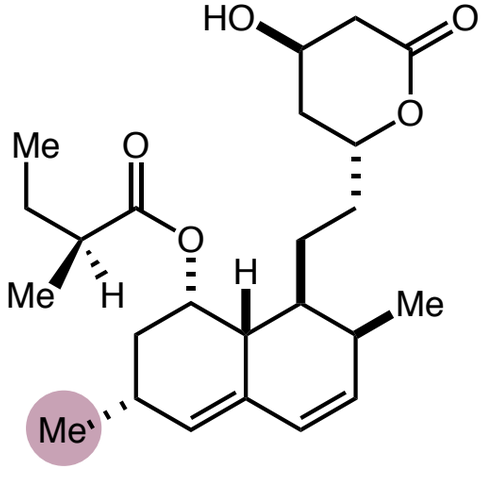
**The so-called Magic Methyl Effect: (a general definition)**

"a rare but welcome phenomenon" where installation of a methyl group on a drug candidate leds to an increase in potency

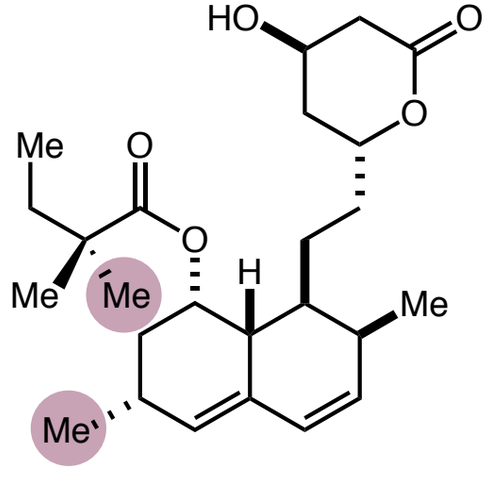
*~a large emphasis on the drastic change in conformation, hence, binding affinity*




**mevastatin**
$IC_{50}$ $HMG\text{-}CoA_R$ = 5.6 nM




**lovastatin**
$IC_{50}$ $HMG\text{-}CoA_R$ = 2.2 nM




**simvastatin**
$IC_{50}$ $HMG\text{-}CoA_R$ = 0.9 nM

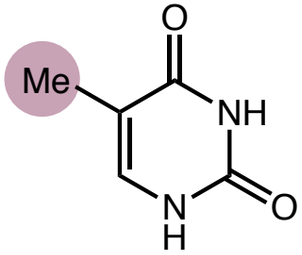
"The methyl group, so often considered as ***chemically inert***, is able to alter deeply the pharmacological properties of a molecule."

Bazzini, P.; Wermuth, C. G. In *The Practice of Medicinal Chemistry;* Academic Press: San Diego, 2008; pp 431-418.

"In comparison to its importance to the pharmaceutical industry, the methyl group is, in our opinion, underrepresented in recent synthetic chemistry.

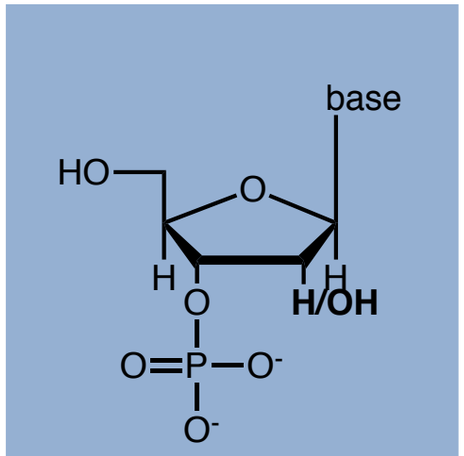
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

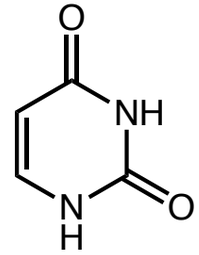
## The Benign Methyl Group - DNA vs RNA




thymine

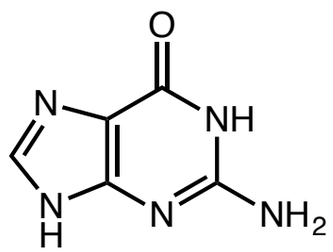
**DNA**



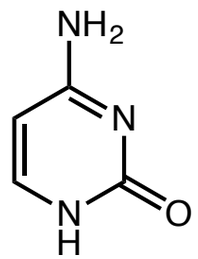




uracil

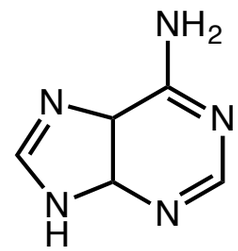
**RNA**




guanine




cytosine



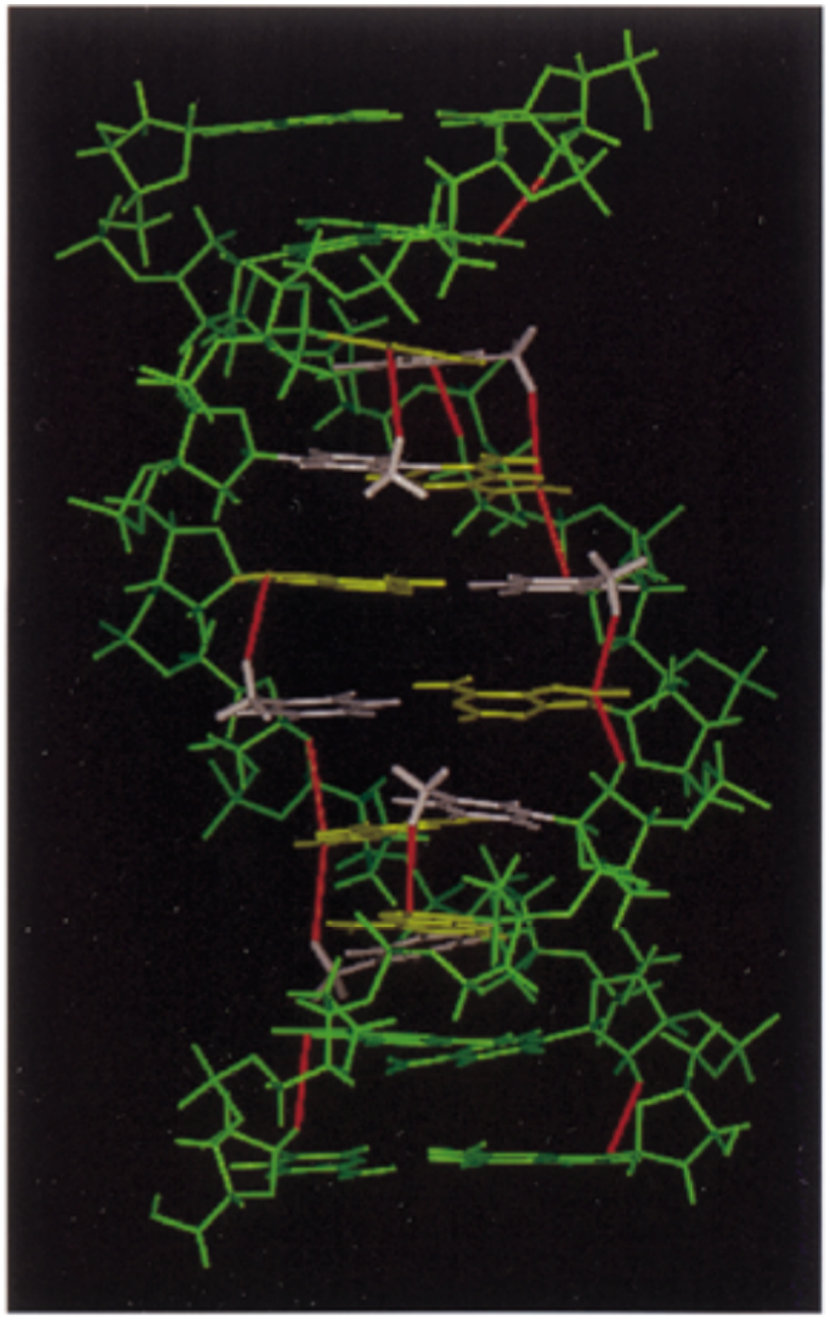

adenine

- CH/π-interaction has been studied for Me and purine oligonucleotides to show appreciable change in DNA strand stiffness (important for enzyme recognition of DNA)

Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665.
Umezawa, Y.; Nishio, M. *Nucleic Acids Res.* **2002**, *30*, 2183.

*Demystifying the Magic Methyl Effect*

## The Benign Methyl Group - DNA vs RNA

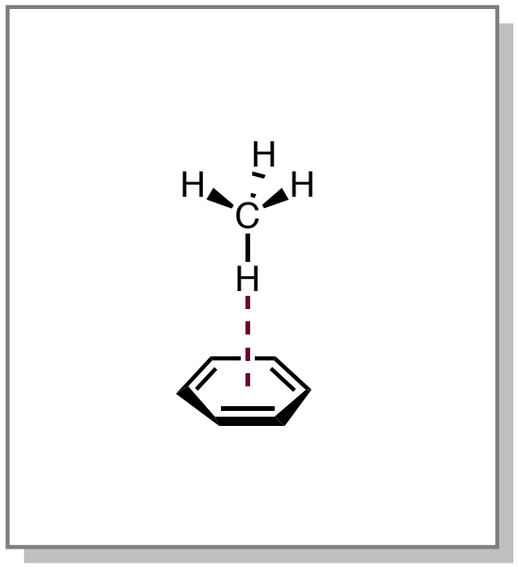


- yellow = adenine
- gray = thymine
- red = CH/π-interaction


Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665.
Umezawa, Y.; Nishio, M. *Nucleic Acids Res.* **2002**, *30*, 2183.

## The Benign Methyl Group - CH/π-interactions

**CH/π-interactions**




π(donor) ⟶ σ*(acceptor)

Via CH/π-interactions: methyl groups have a greater chance to be involved in an interaction compared to OH due to:

- more (three) hydrogens
- multiple simultaneous interactions possible
- additive free energy effects

Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665.
Umezawa, Y.; Nishio, M. *Nucleic Acids Res.* **2002**, *30*, 2183.

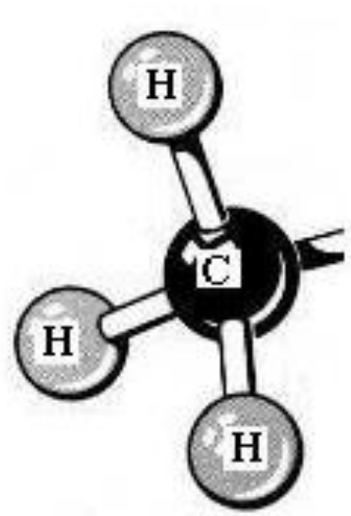
*Demystifying the Magic Methyl Effect*

## Modes of Action

***a combination of.....***

**Solubility**

**Conformation**



methyl group

**Binding Interactions**

**Metabolism**

***later.....***

**Current Synthetic Methods**

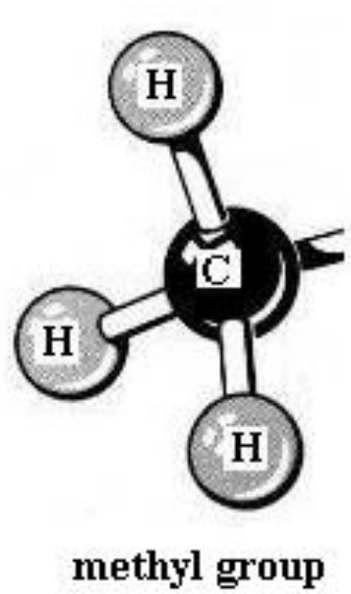
*Demystifying the Magic Methyl Effect*

## Modes of Action

***a combination of.....***

**Solubility**

**Conformation**



methyl group

**Binding Interactions**

**Metabolism**

---

***later.....***

**Current Synthetic Methods**

# *Demystifying the Magic Methyl Effect*

## ■ Solubility

General solubility for increased bioavailability

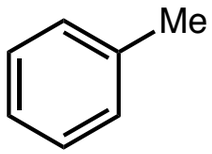
### Lipophilicity

*"lipid loving", hydrophobic*

**benzene**

Log *P* = 2.13

**toluene**

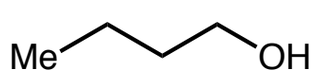



Log *P* = 2.69

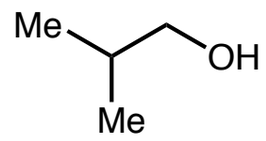
Log *P* is logarithm of the partition coefficient between n-octanol and water

■ important for crossing biomembranes to get to target tissues and for transport through bloodstream

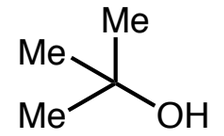
### Hydrophilic Effect



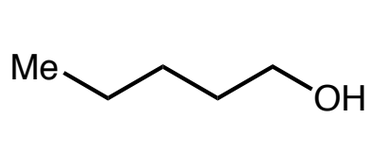

*n*-butanol
8.2g/100g $H_2O$



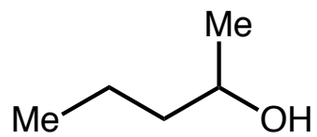

isobutanol
5g/100g $H_2O$



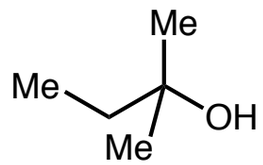

*tert*-butanol
miscible



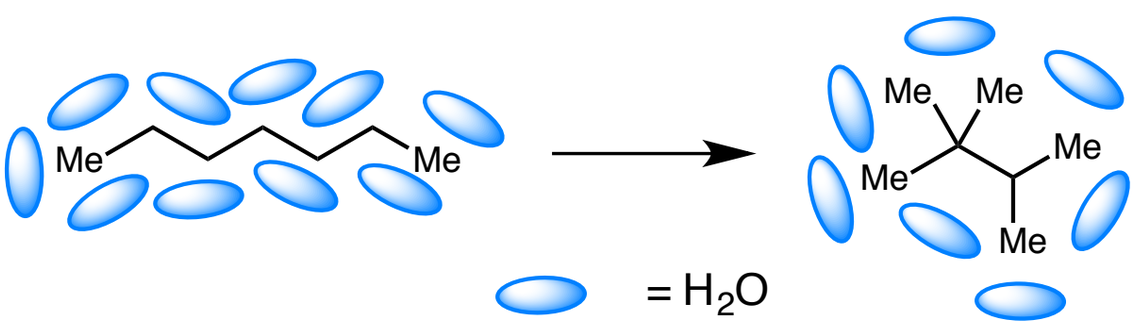

*n*-pentanol
2.4g/100g $H_2O$




2-pentanol
4.9g/100g $H_2O$




neopentanol
12.2g/100g $H_2O$




■ fewer water molecules needed to be organized, entropic gain with "globular" shape

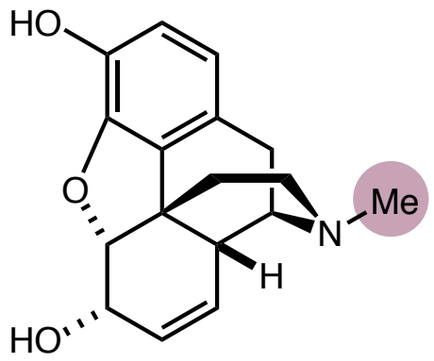
■ more negative $\Delta G_{desolvation}$ when transitioning from aqueous to membrane

Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

# *Demystifying the Magic Methyl Effect*

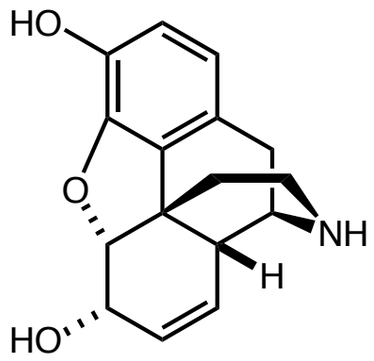
- Lipophilicity to increase bioavailability

***Placement of methyl groups is important:***



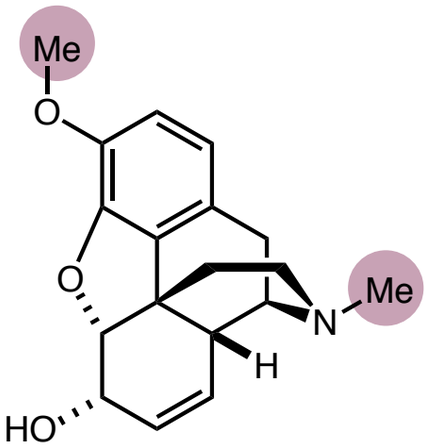

**morphine**

structure elucidated by Sir Robert Robinson




**normorphine**

6-fold reduction in in vivo analgesic activity




**codeine**

3-fold reduction in in vivo analgesic activity, 200-fold reduction in receptor affinity

- dominant ionic interactions for drug catalytic site still maintained

- more polar nitrogen moiety, harder to pass through blood-brain barrier

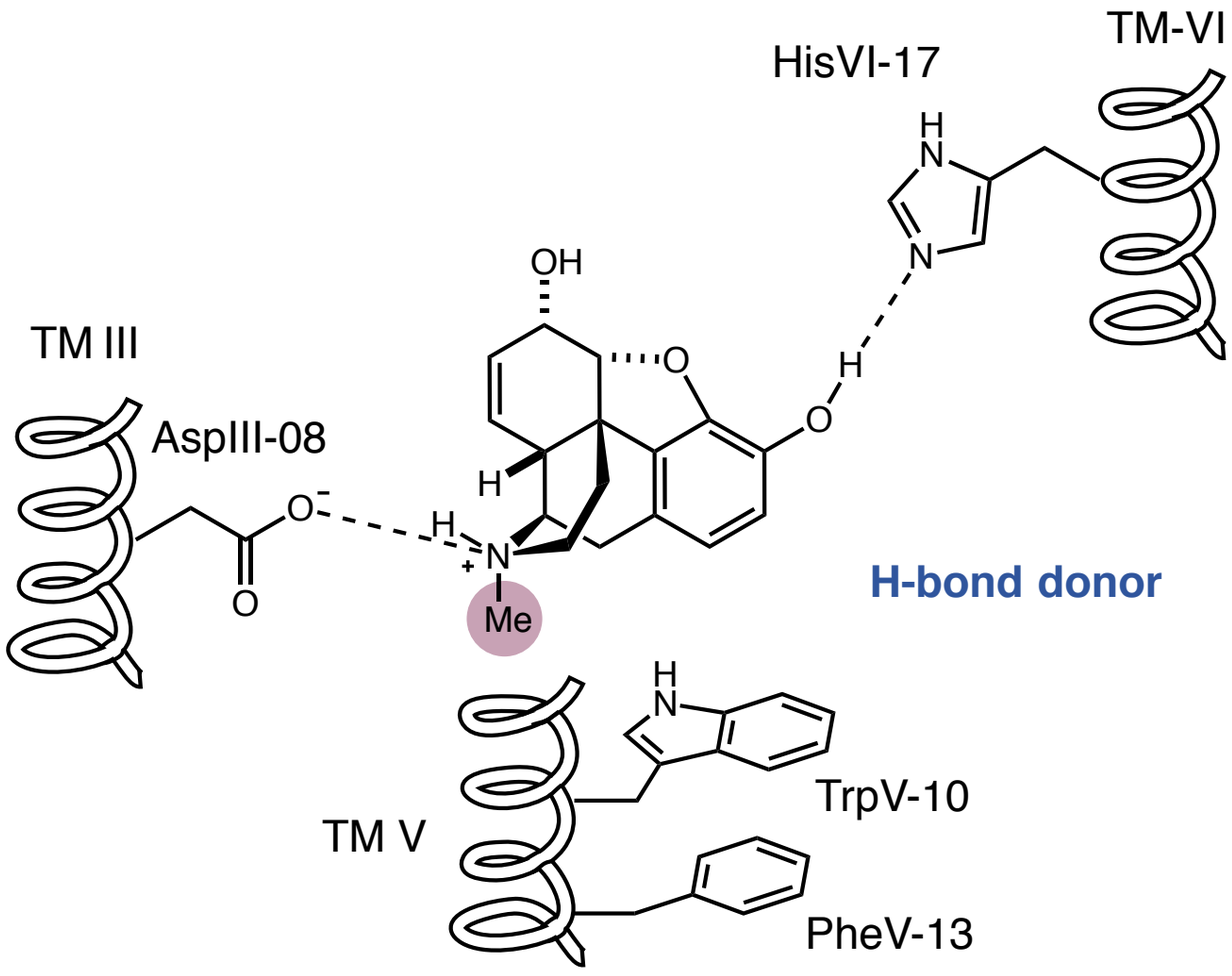
Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

# *Demystifying the Magic Methyl Effect*

- Lipophilicity to increase bioavailability

***Placement of methyl groups is important:***

*TM = transmembrane domain*




- ionic interaction with aminium cation and carboxylate
- H-bond interaction
- van der Waals interactions

Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

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■ Lipophilicity to increase bioavailability

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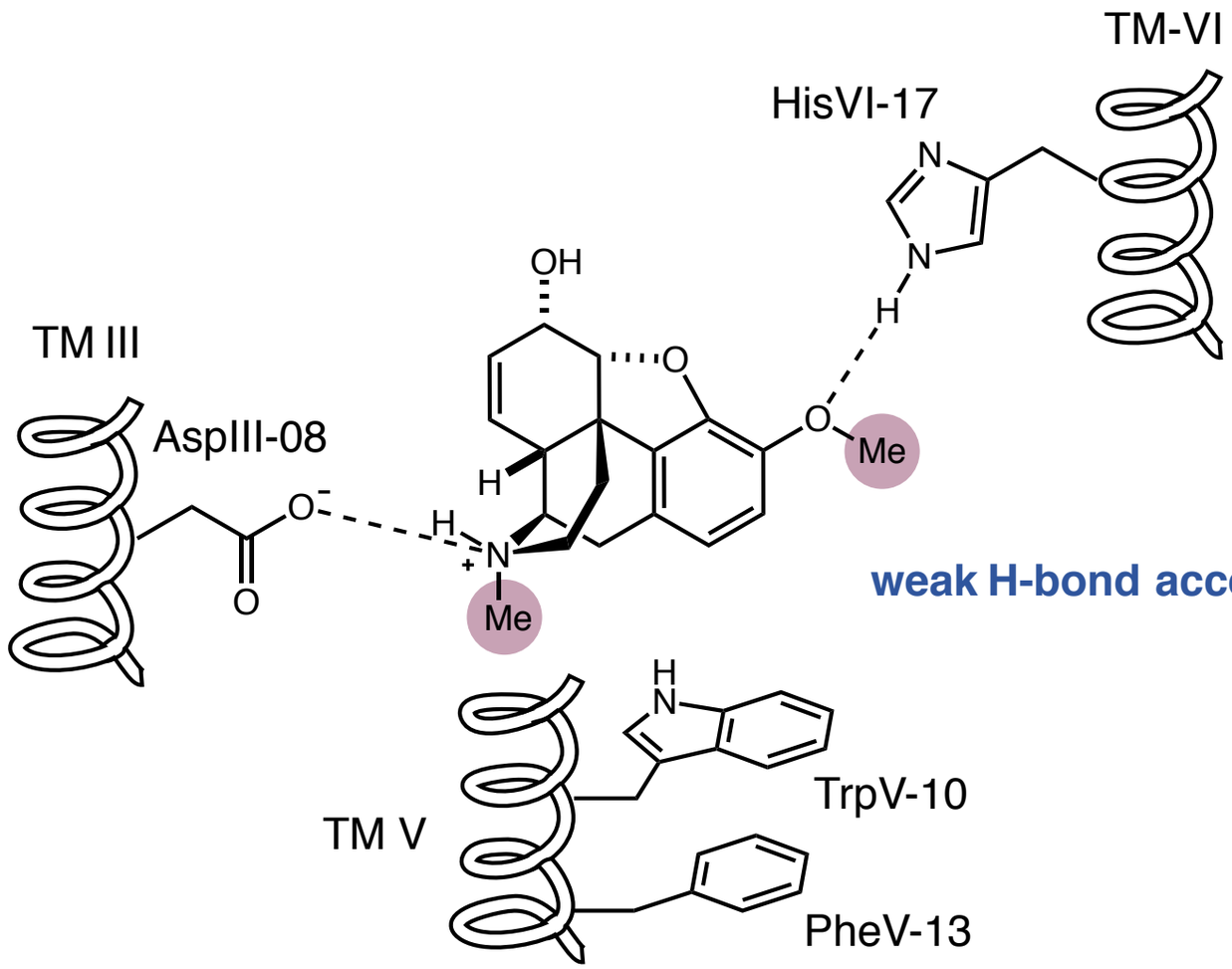


**weak H-bond acceptor**

■ dominant ionic interactions for drug catalytic site still maintained

■ weaker H-bond interaction causes 200-fold reduction in receptor binding

■ codeine gets metabolized to morphine

Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

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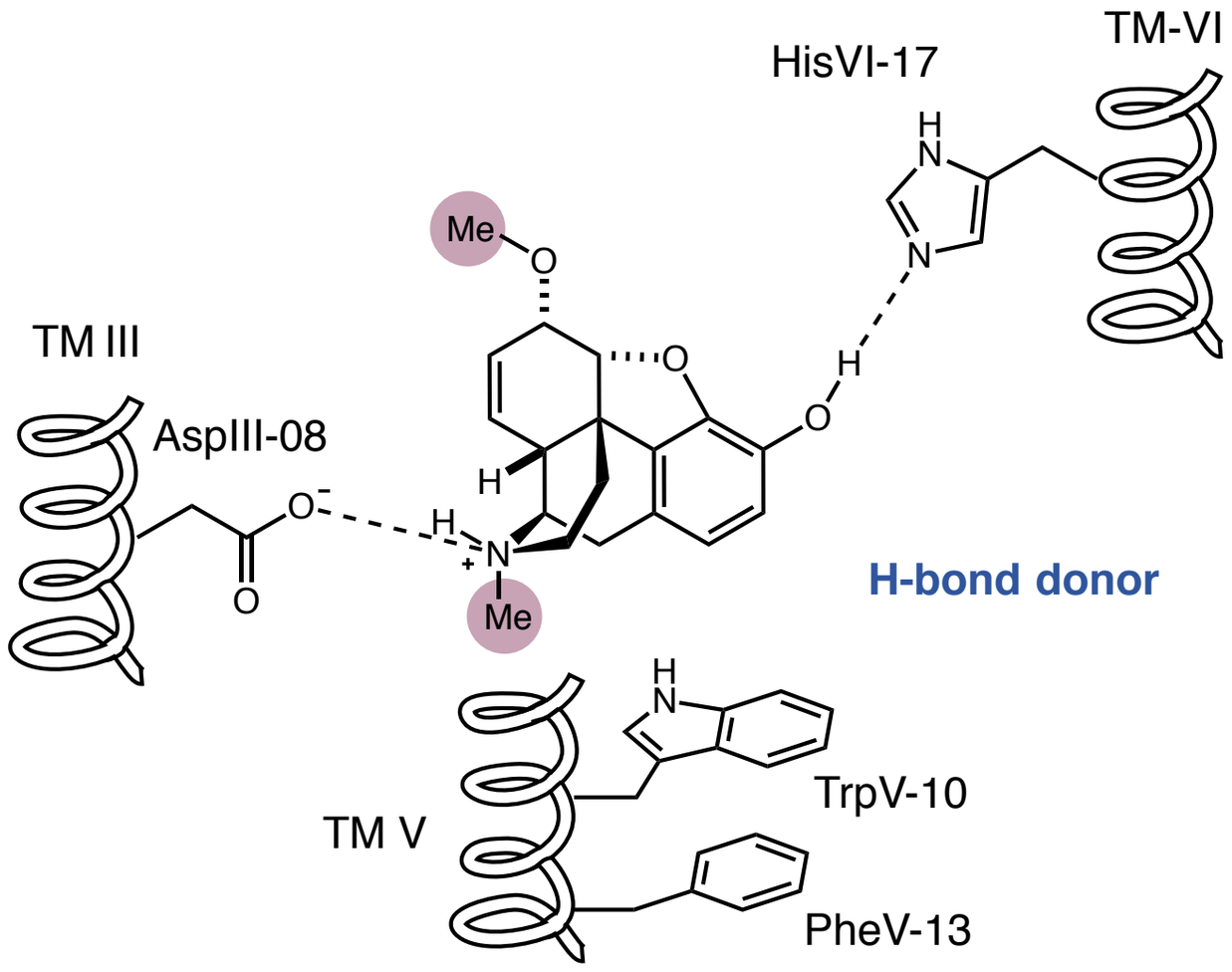
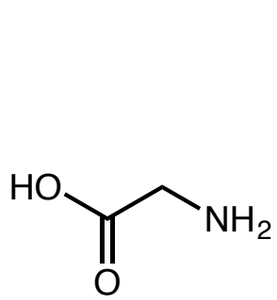



- heterocodeine has a 2-fold increase in in vivo activity
- H-bond interaction
- methyl allyic ether aids in ***solubility***, hence, passage through central nervous system

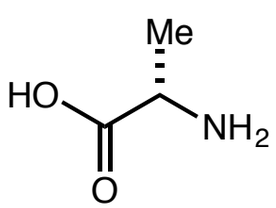
Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

# *Demystifying the Magic Methyl Effect*

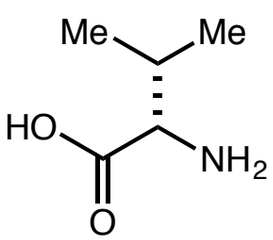
- Free energy of desolvation
  - more -$CH_3$ groups leads to more spontaneous transfer from aqueous to protein layer



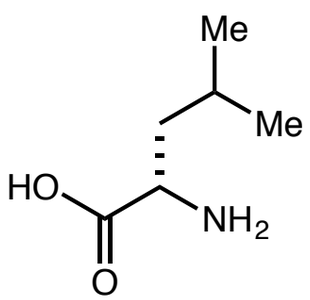
glycine



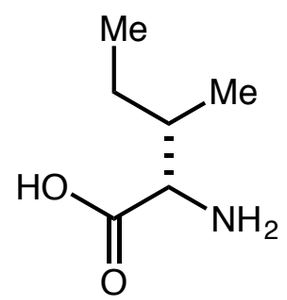
alanine



valine



leucine

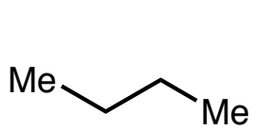


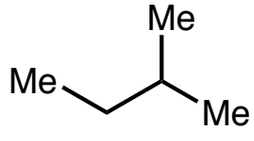
isoleucine

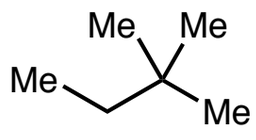
| | glycine | alanine | valine | leucine | isoleucine |
|---|---|---|---|---|---|
| $\Delta G_{transfer}$ kcal/mol= | | -1.3 (-0.73) | -1.9 (-1.69) | -1.9 (-2.42) | -1.9 (-2.97) |

( ) = side chain contribution moving from water to ethanol

**increasing methyls, decreasing $\Delta G_{desolvation}$**







- $\Delta\Delta G_{transfer}$ of C-H to C-$CH_3$ = 0.8 kcal/mol
- theoretical ~3.5 fold boost in potency from methylation


Andrews, P. R.; Craik, D. J.; Martin, J. L. *J. Med. Chem.* **1984**, *27*, 1648-1657.
Nemethy, G. *Angew. Chem. Int. Ed.* **1967**, *6*, 195-206.
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

# *Demystifying the Magic Methyl Effect*

- The bigger picture of methylation and potency improvements

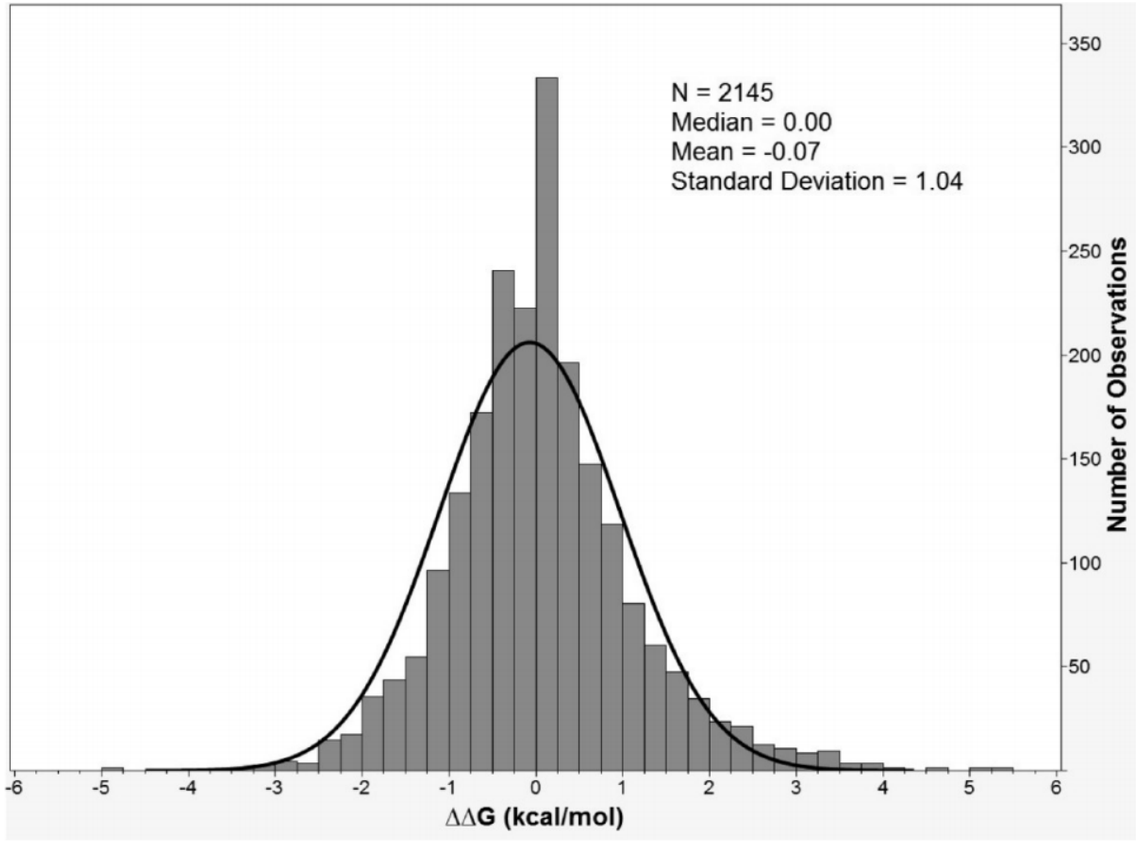



**Figure 1.** Distribution of free energy changes on activity for substitutions of a hydrogen atom by a methyl group in publications in the *Journal of Medicinal Chemistry* and *Bioorganic Medicinal Chemistry Letters* during 2006–2011.

- methylation just as likely to decrease binding affinity as it is to increase
- rare for addition of Me group to give free energy gain greater than 3 kcal/mol (4 cases, 0.0019%
- 10 fold boost (1.36 kcal/mol) - 8%
- 100 fold boost (2.7 kcal/mol) - 0.4%


Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2012**, *55*, 4489-4500.
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

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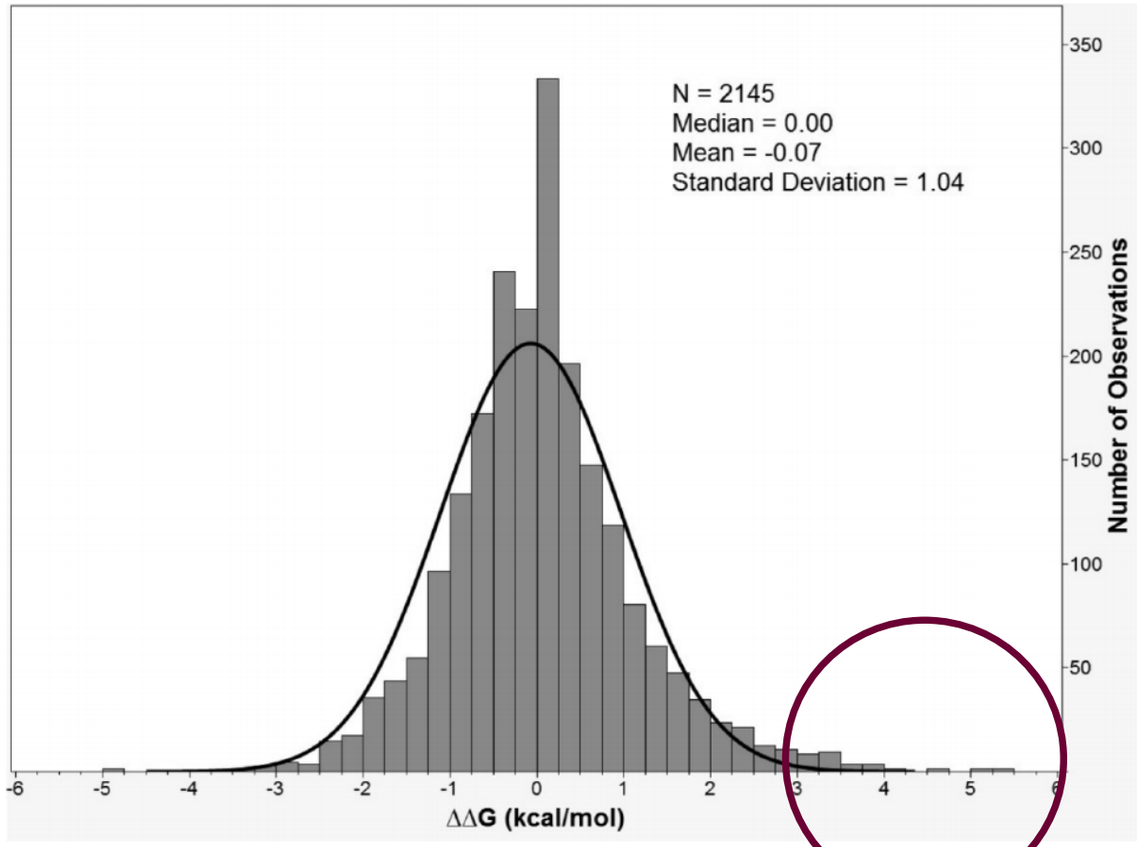



**Figure 1.** Distribution of free energy changes on activity for substitutions of a hydrogen atom by a methyl group in publications in the *Journal of Medicinal Chemistry* and *Bioorganic Medicinal Chemistry Letters* during 2006–2011.

**Magic Methyl Effect - free energy gain from Me addition is or above what is predicted**


Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2012**, *55*, 4489-4500.
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

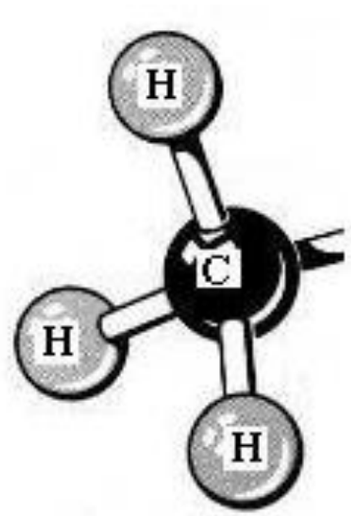
# *Demystifying the Magic Methyl Effect*

■ How do you invoke the Magic Methyl Effect?

***a combination of.....***

**Solubility**

**Conformation**



methyl group

**Binding Interactions**

**Metabolism**

*Demystifying the Magic Methyl Effect*

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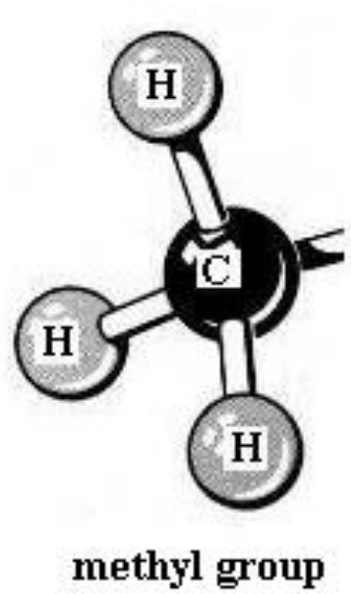
**Solubility**

**Conformation**



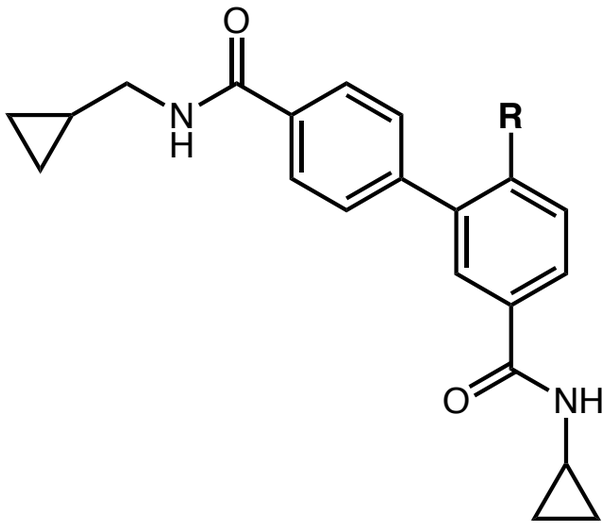
methyl group

**Binding Interactions**

**Metabolism**

# *Demystifying the Magic Methyl Effect*

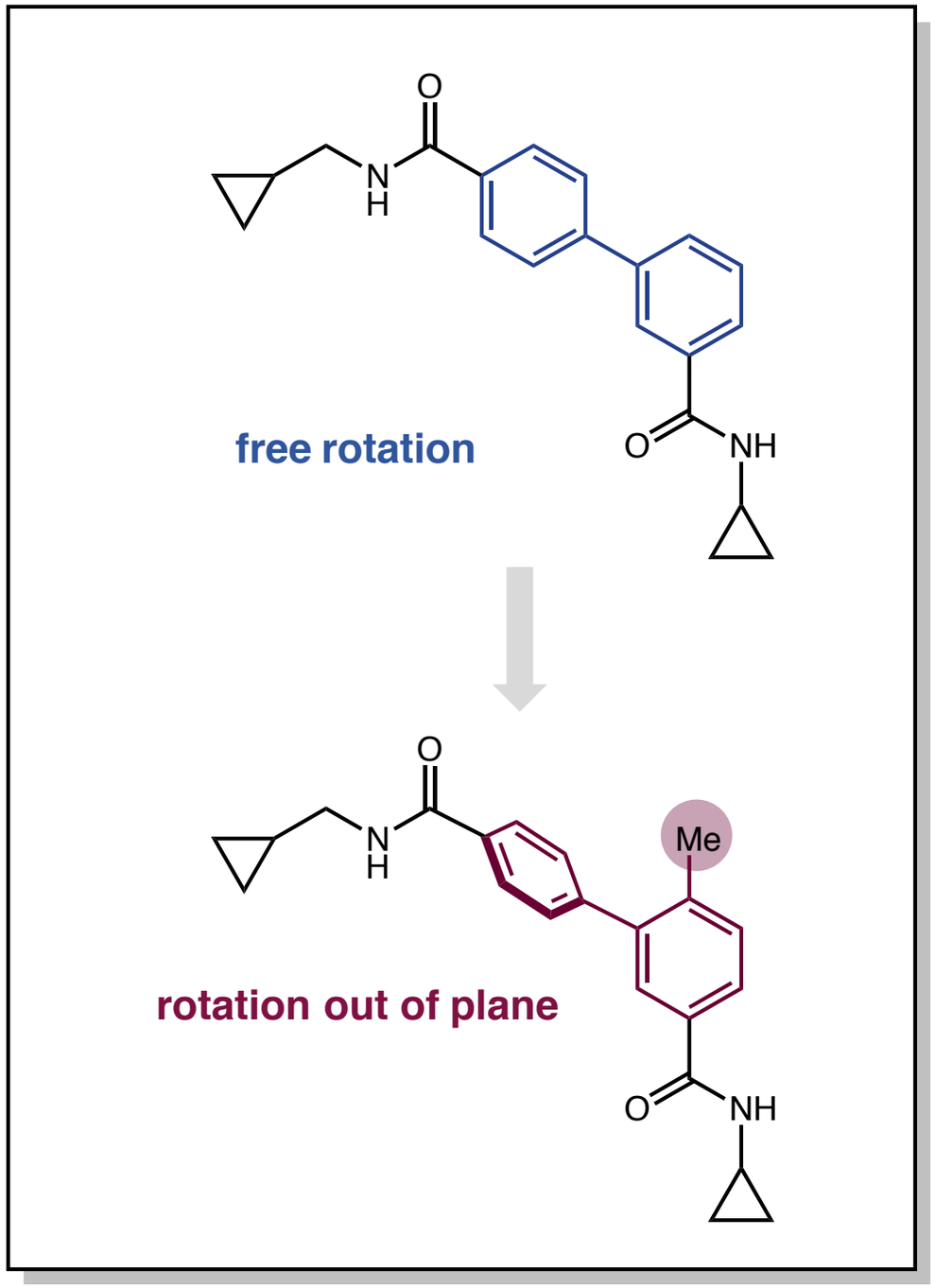
- Conformational preorganization leads to ~200-fold boost




**biphenyl amide inhibitors of p38α kinase**

| R | $K_i$ (nM) | $IC_{50}$ |
|---|---|---|
| **H** | >2500 | >16,000 |
| **Me** | **12** | **75** |
| **Cl** | 25 | 160 |
| **F** | 460 | 2900 |
| **OMe** | 520 | 3300 |

*(inhibitor constant, nM needed to achieve 1/2 max inhibition)*




Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2012**, *55*, 4489-4500.
Angell, R. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4428-4432.

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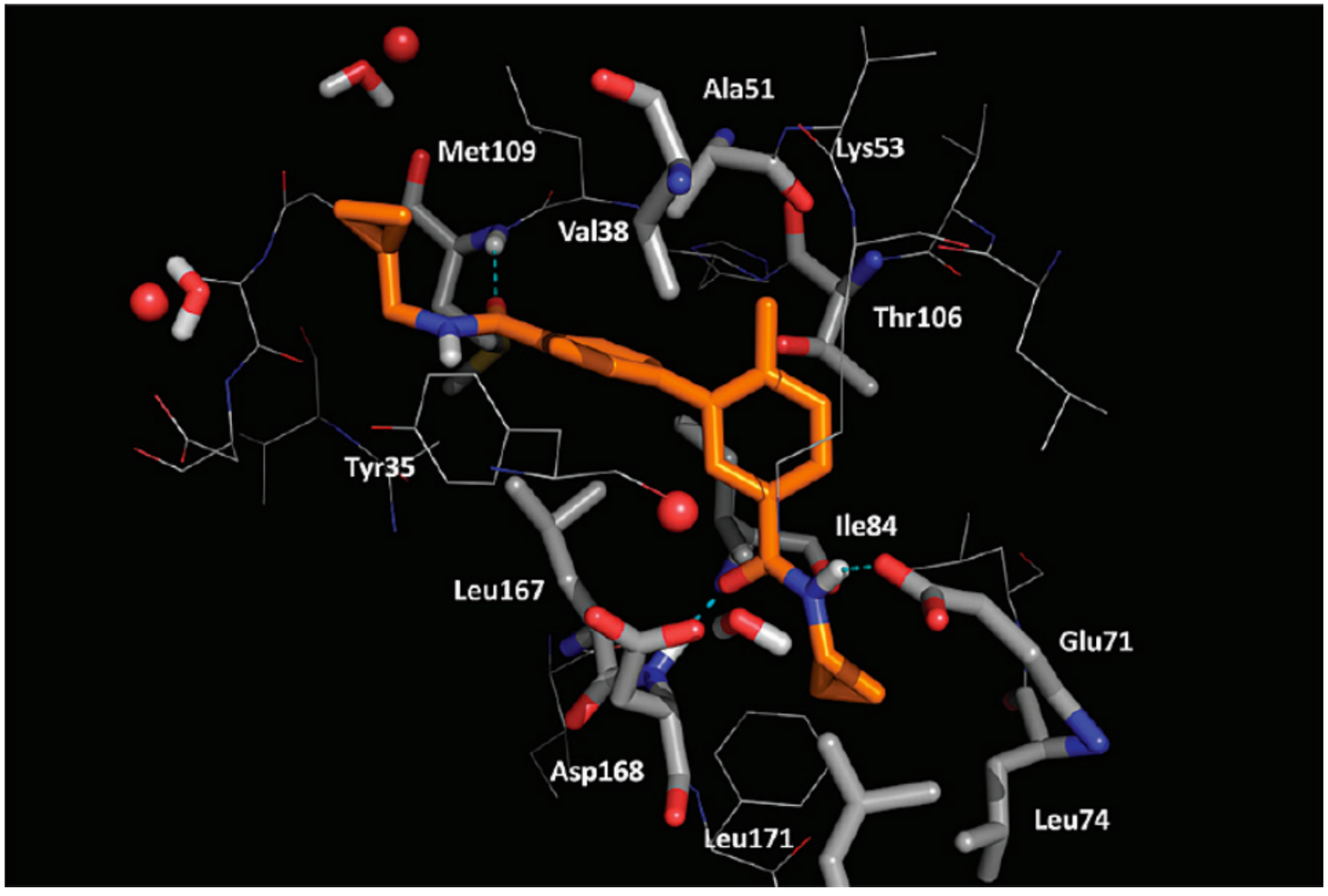


- methyl in lipophilic pocket - larger groups do not fit
- several hydrophobic interactions with biphenyl
- dihedral angle of *o*-Me-biphenyl free drug matches the bound conformer best


Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2012**, *55*, 4489-4500.
Angell, R. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4428-4432.

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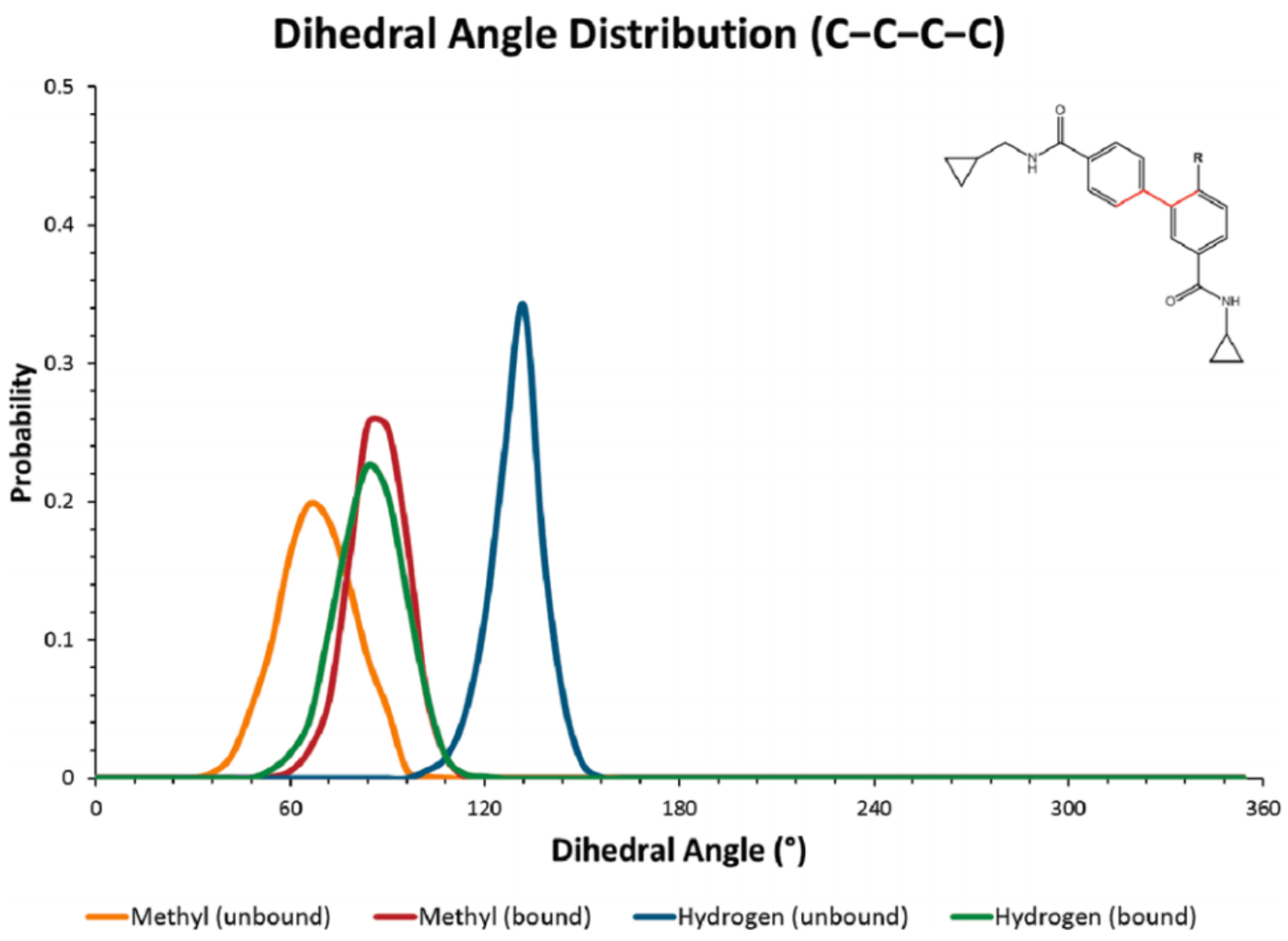





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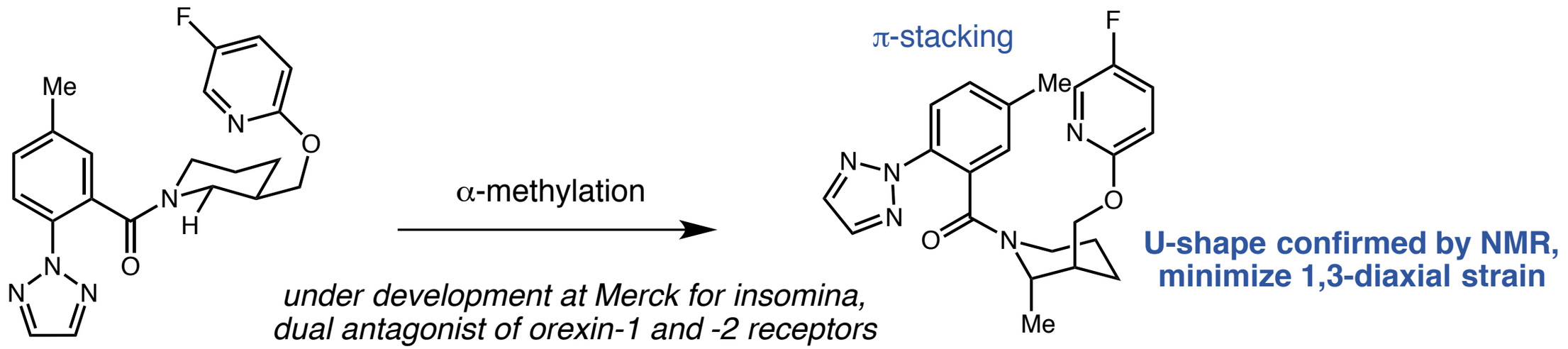
- dihedral angle of *o*-Me-biphenyl free drug matches the bound conformer best


Leung, C. S.; Leung, S. S. F.; Tirado-Rives, J.; Jorgensen, W. L. *J. Med. Chem.* **2012**, *55*, 4489-4500.
Angell, R. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4428-4432.

# *Demystifying the Magic Methyl Effect*

## ■ Conformational preorganization leads to 480-fold boost




*under development at Merck for insomina, dual antagonist of orexin-1 and -2 receptors*

**96 nM** **0.2 nM**

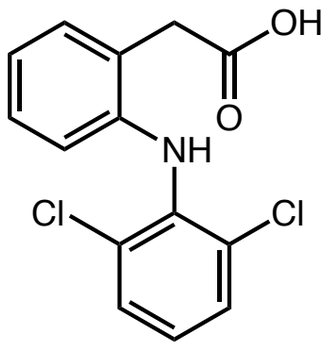
"In terms of value, a methyl group that leads to a profound improvement in potency is hard to beat."

| **If α-substituent is** | |
|---|---|
| F | unstable next to heteroatom, not as much steric influence, change in stereoelectronics |
| $CF_3$ | risk of violating Lipinski's rules: **$CF_3$**: ΔMW= 68 g/mol, Δ*c*logP~0.9, **Me**: ΔMW= 14 g/mol, Δ*c*logP~0.5) |
| larger alkyl groups | too lipophilic, not a good track record of becoming drugs |

Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

# *Demystifying the Magic Methyl Effect*

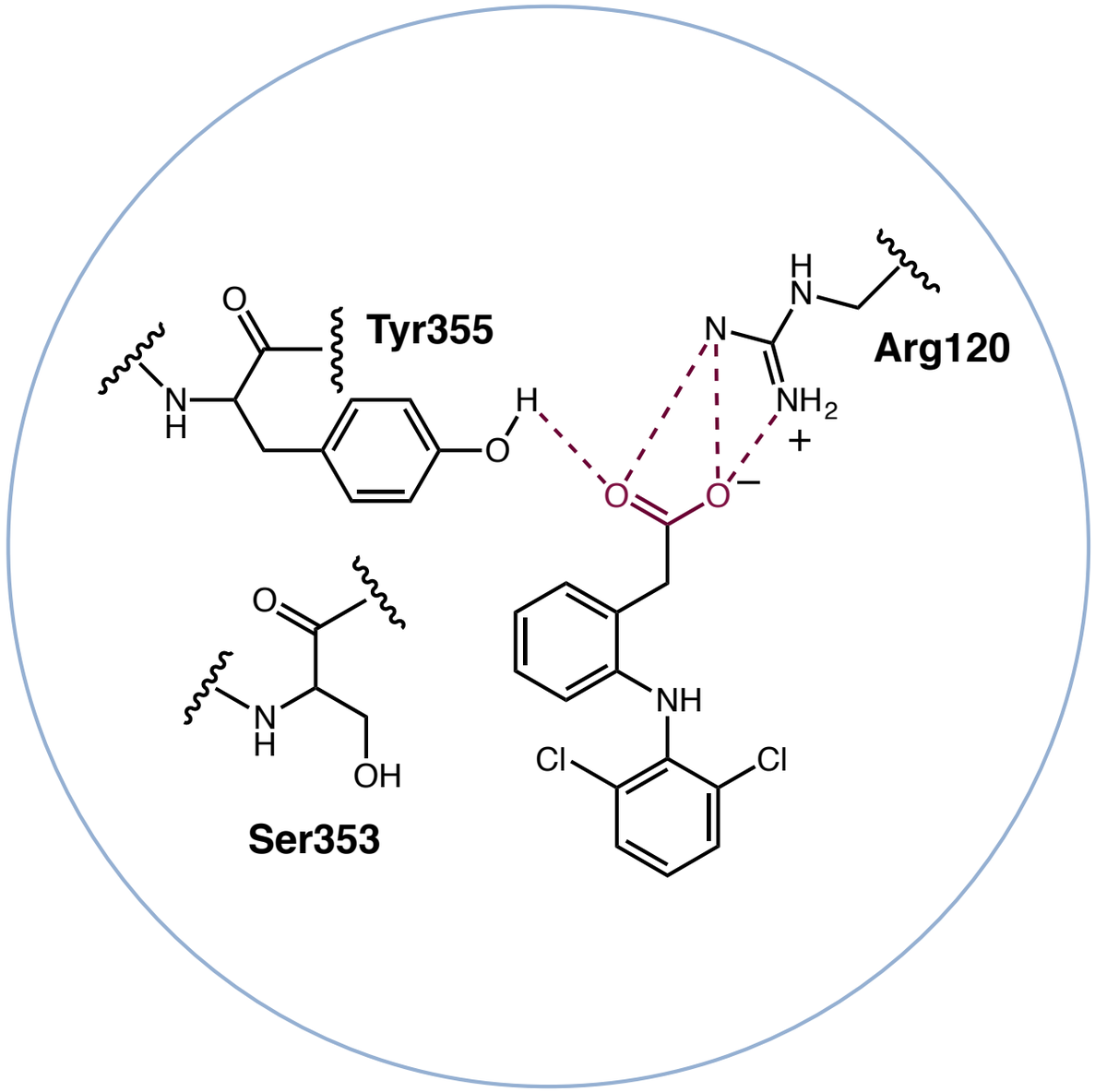
■ Use of methyl group to decrease binding affinity




**diclofenac**

$K_i$ (μM) COX-1 = 0.01
$K_i$ (μM) COX-2 = 0.01

**NSAID**




Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

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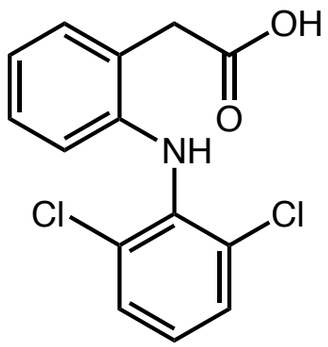


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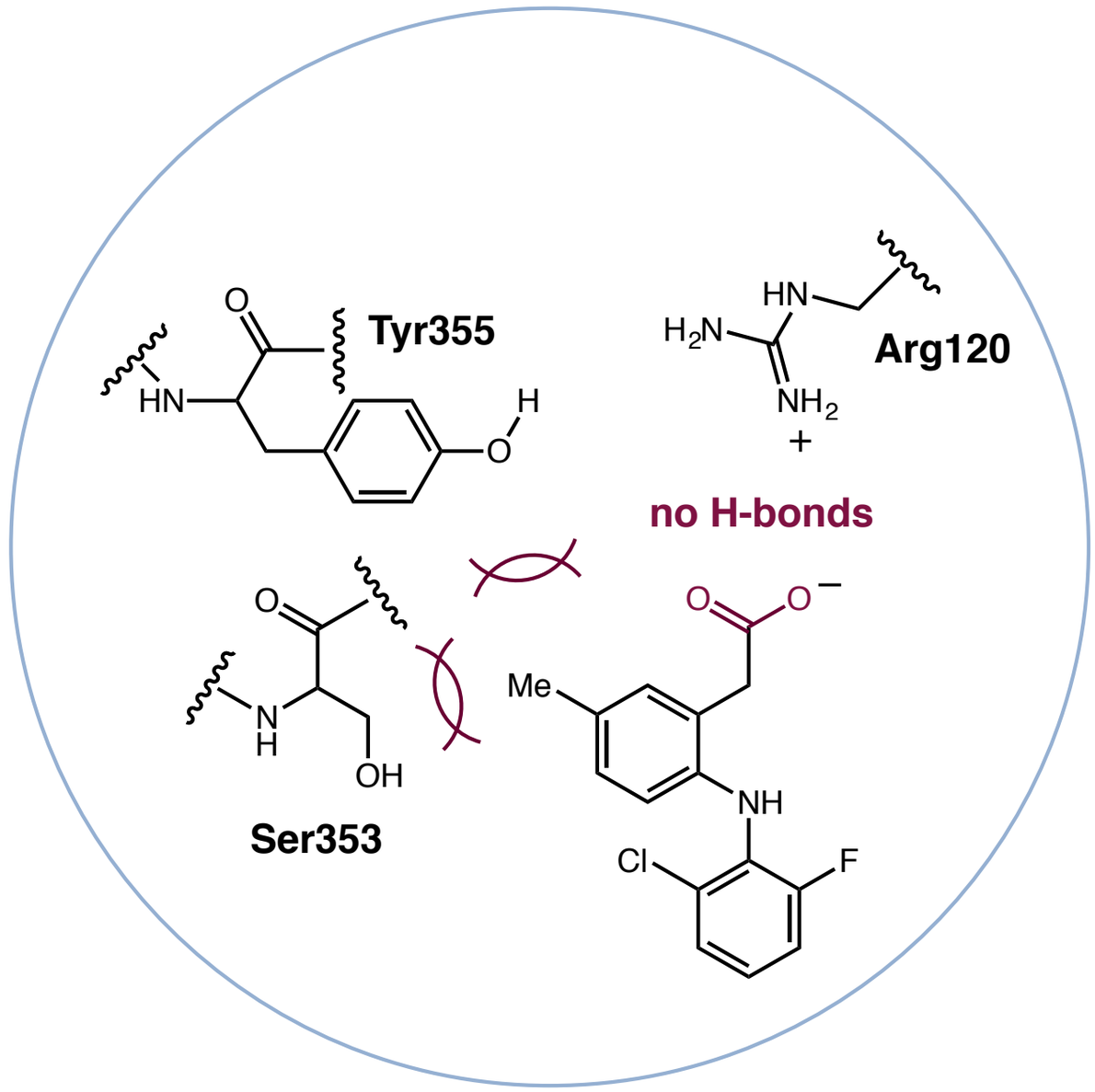
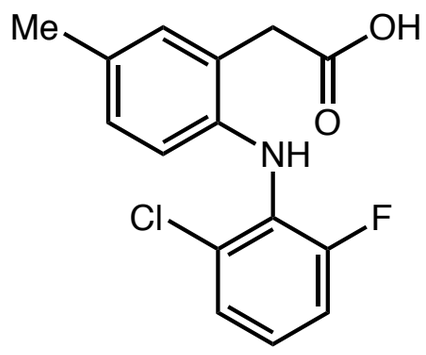



**lumiracoxib**

$K_i$ (μM) COX-1 = 3.2
$K_i$ (μM) COX-2 = 0.06

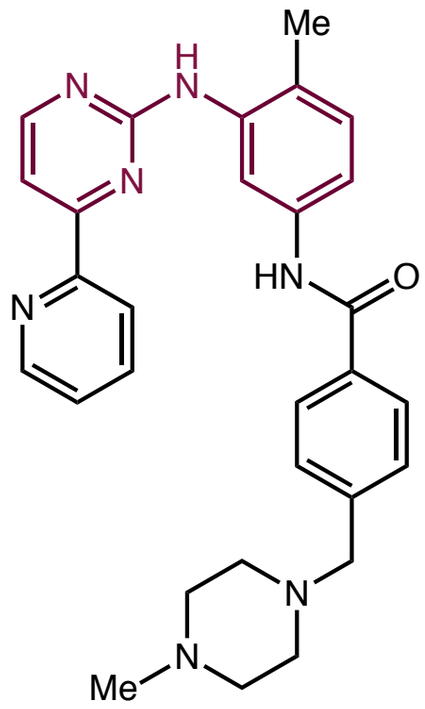
*NSAID, but taken off market due to liver damage*

Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

# *Demystifying the Magic Methyl Effect*

- Methyl group installation around freely rotating bonds

**"rationally developed" -**
***combichem*-HTS drug discovery tactic**




**imatinib - Novartis**
*treats chronic myelogenous leukemia*
*by inhibiting Bcr-Abl kinase*

- Patients live up to 5 years longer
- very minimal side effects
- *Bcr-Abl* kinase responsible for cell growth of cancer cells
- first tyrosine-kinase inhibitor on market


Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nature Rev. Drug Discovery* **2002**, *1*, 493.
Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

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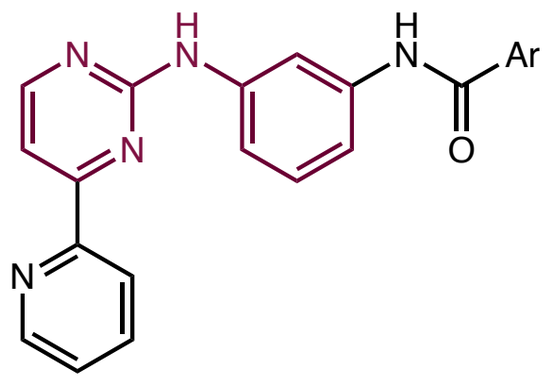
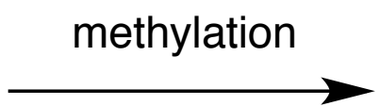
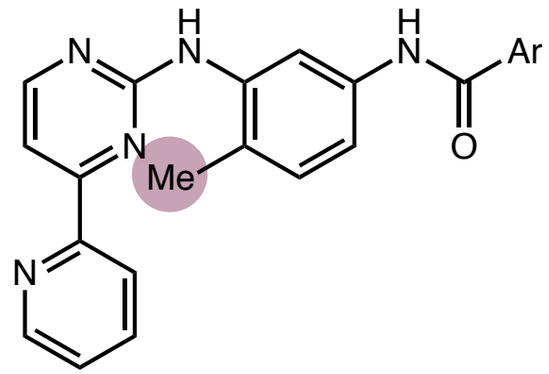



PKA, TK and Bcr-Ablk inhibitor

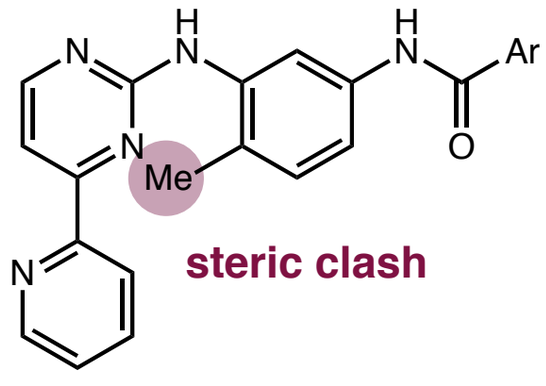
*HTS to get scaffold*



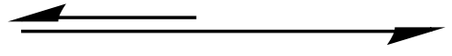



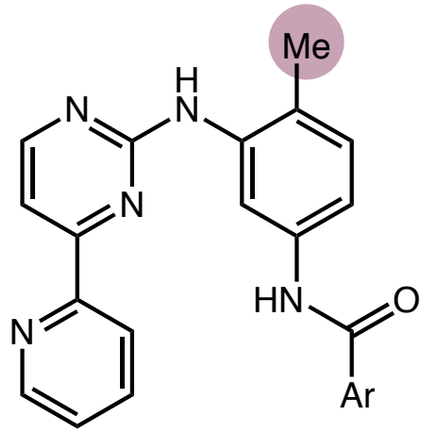

Bcr-Ablk selectivity over PKC

***Conformers:***




**steric clash**



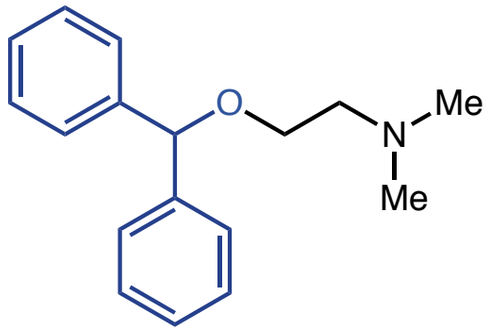



confirmed by X-ray diffraction


Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. *Nature Rev. Drug Discovery* **2002**, *1*, 493.

Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

- A change in conformation isn't everything




**diphenhydramine**

**Benadryl**

antihistamines tend to be **rigid**


Bazzini, P.; Wermuth, C. G. In *The Practice of Medicinal Chemistry;* Academic Press: San Diego, 2008; pp 431-418.
Harms, A. F.; Nauta, W. Th. *J. Med. Chem.* **1959**, *2*, 57-77.

# *Demystifying the Magic Methyl Effect*

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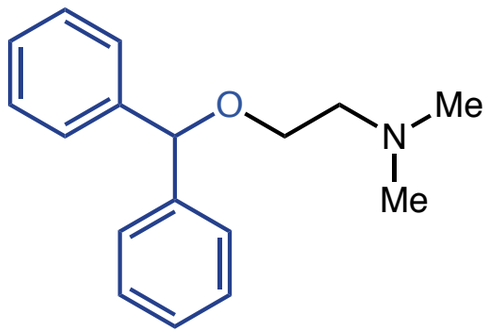


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**Benadryl**

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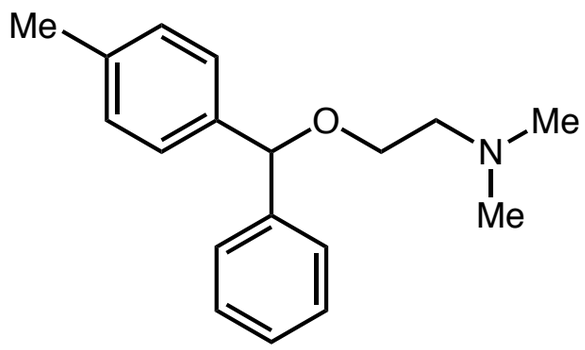
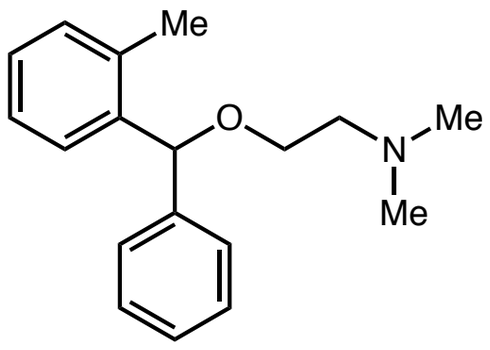



**diphenhydramine**

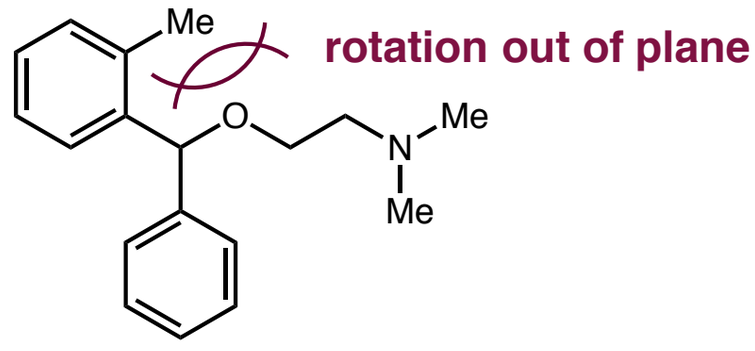
**Toladryl**

*3.7-fold increase in activity*

*2.5-fold decrease in anticholine activity*




**Orphenadrine**




*5-fold reduction in activity*

*2.1-fold increase in anticholine activity*

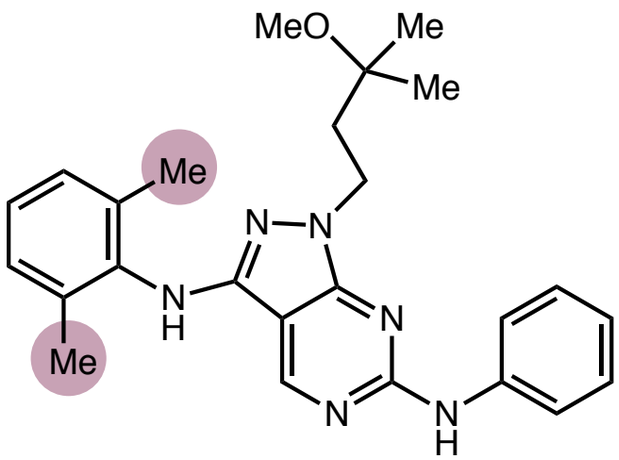

Bazzini, P.; Wermuth, C. G. In *The Practice of Medicinal Chemistry;* Academic Press: San Diego, 2008; pp 431-418.

Harms, A. F.; Nauta, W. Th. *J. Med. Chem.* **1959**, *2*, 57-77.

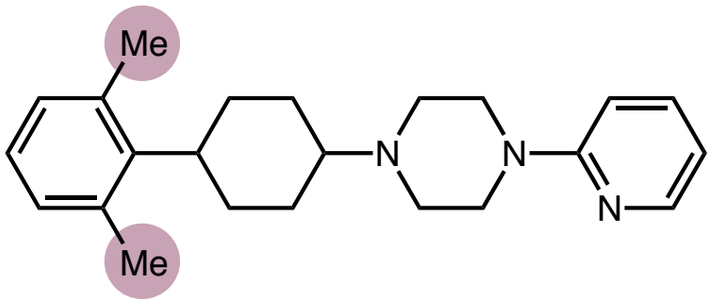
# *Demystifying the Magic Methyl Effect*

■ Overview of where to place Me groups for most impact

## *ortho* substitution

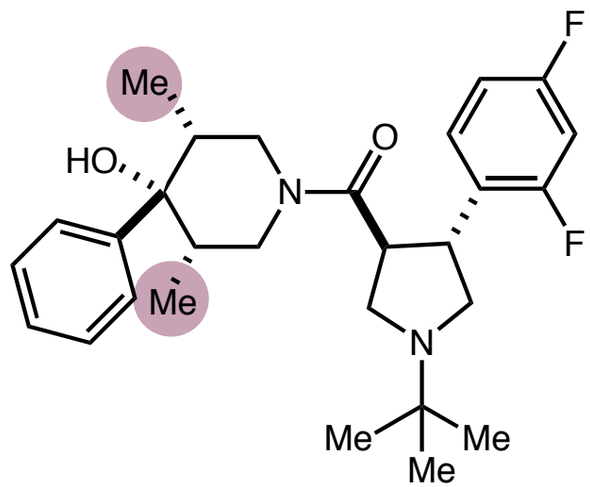



**1333-fold boost**

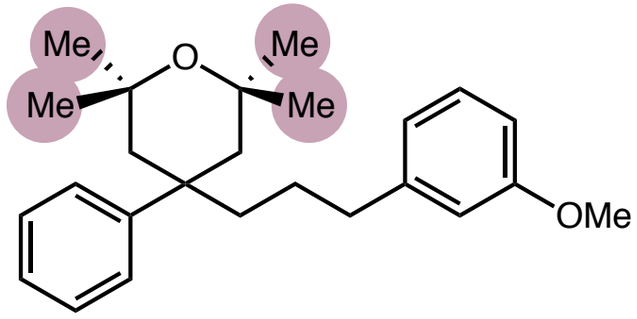



**159-fold boost**

## on substituted alkyl rings

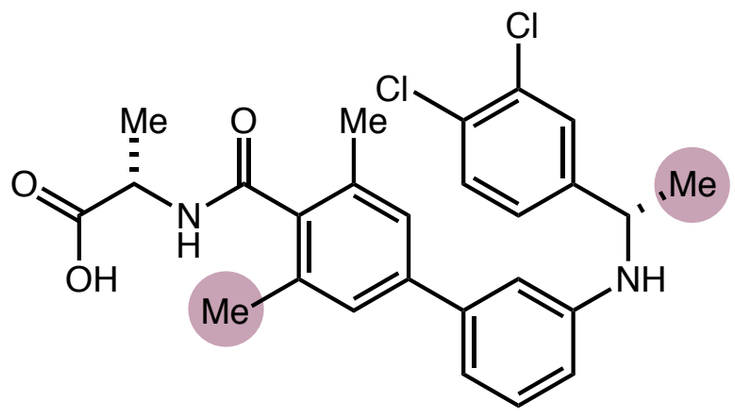



**97-fold boost**

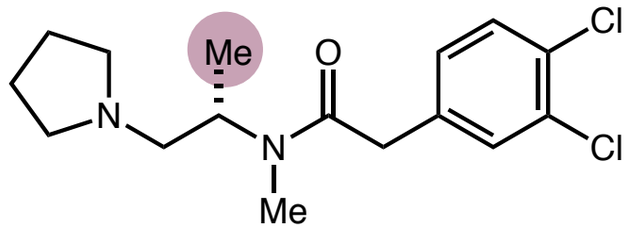



**598-fold boost**

## around two freely rotatable bonds




**2135-fold boost**




**480-fold boost**

Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

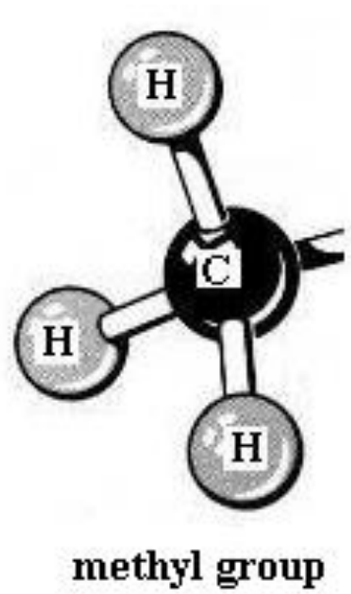
# *Demystifying the Magic Methyl Effect*

- How do you invoke the Magic Methyl Effect?

***a combination of.....***

**Solubility**

**Conformation**



methyl group

**Binding Interactions**

**Metabolism**

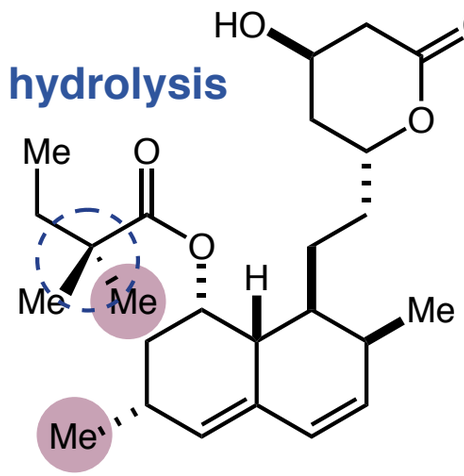
# *Demystifying the Magic Methyl Effect*

## ■ Prevention and enhancement of drug metabolism

### Methyl Groups as Protecting group

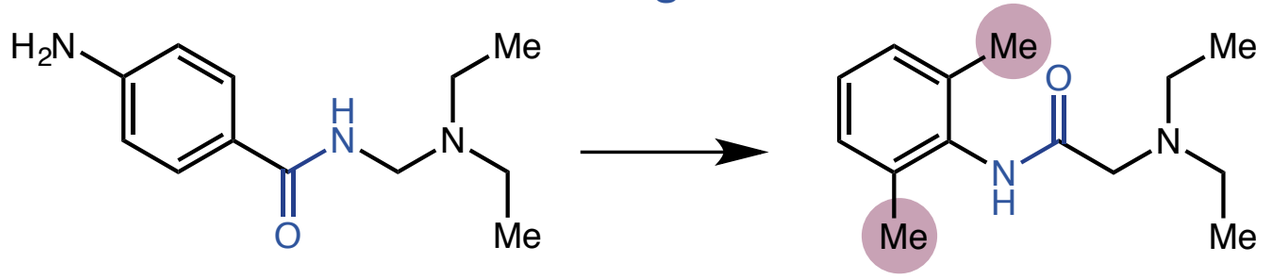
***Protection of adjacent functional group:***

**prevention of hydrolysis**




**simvastatin**

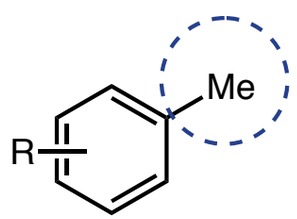
**plasmatic amidases cleavage blocked**

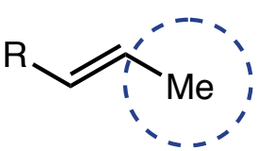


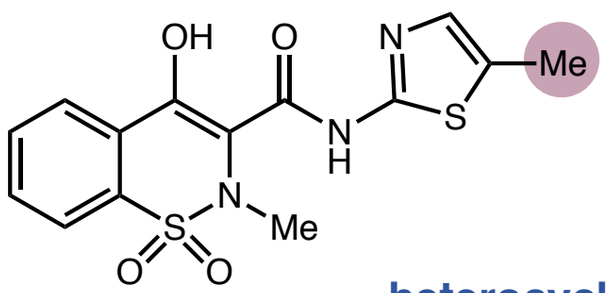

**procainamide** **lidocaine**

### Methyl Groups as a Metabolic Soft Spot

***Change in half-life:***



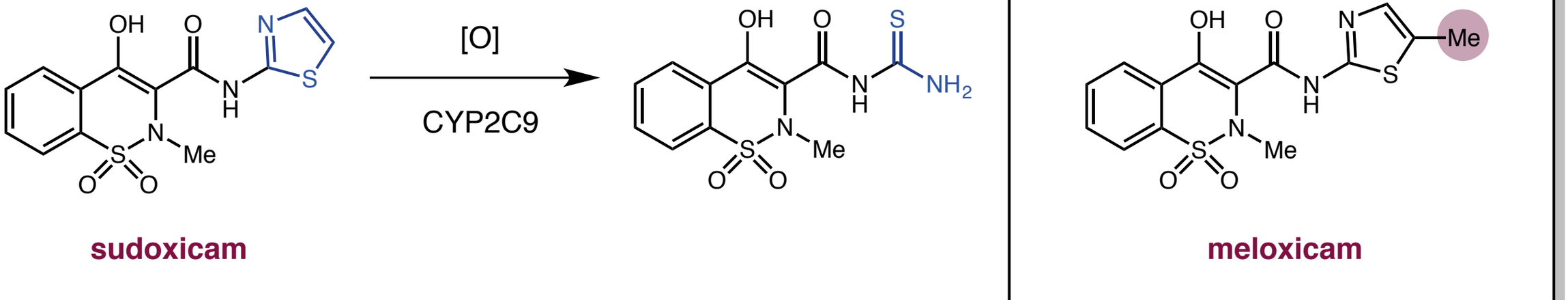




**meloxicam**

**heterocycle susceptible to oxidation**

Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

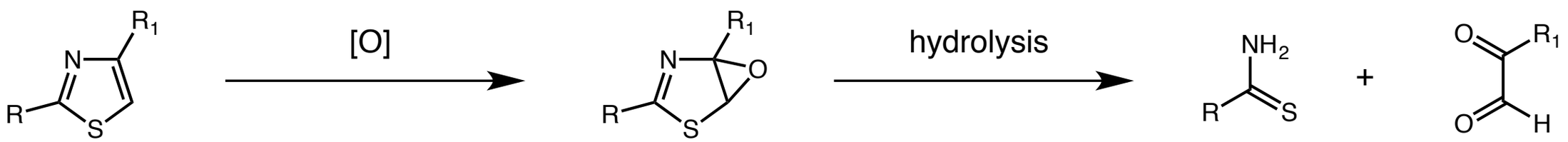
## Prevention and enhancement of drug metabolism




**sudoxicam**

**meloxicam**

## Mechanism of metabolization of thiazole derivatives

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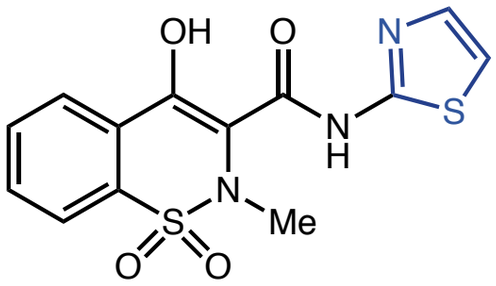
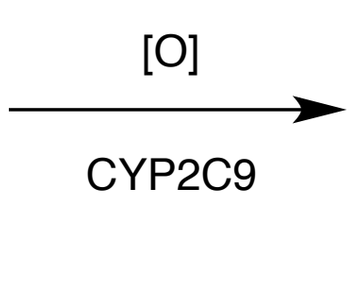
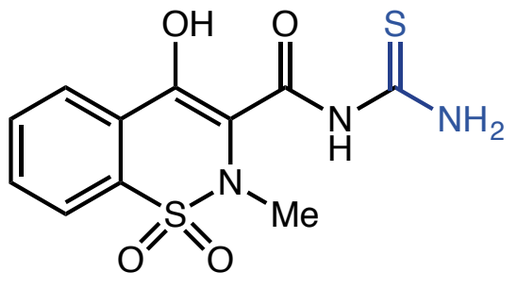
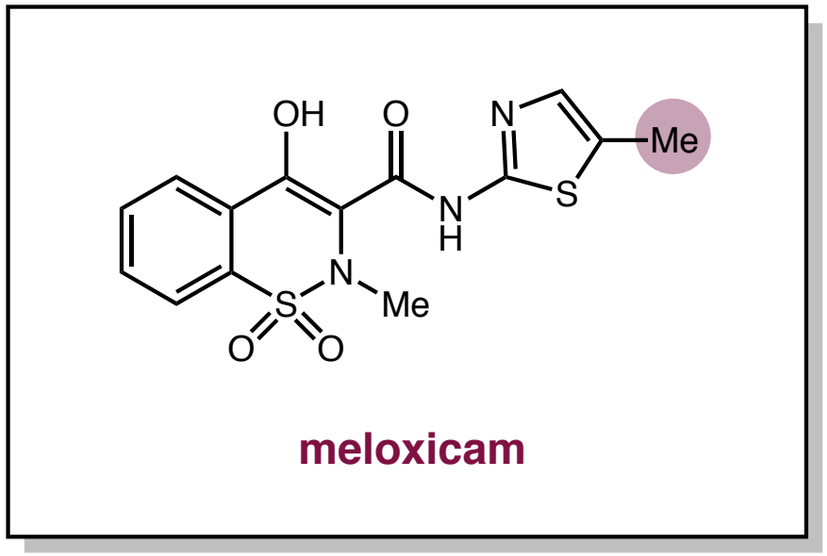



**sudoxicam**

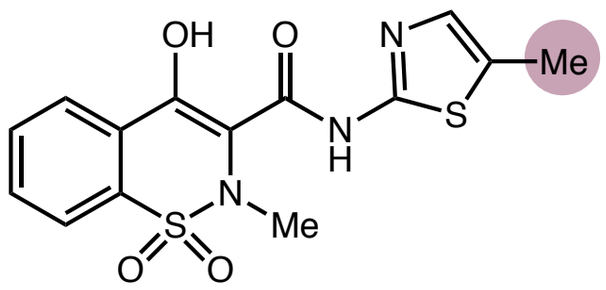


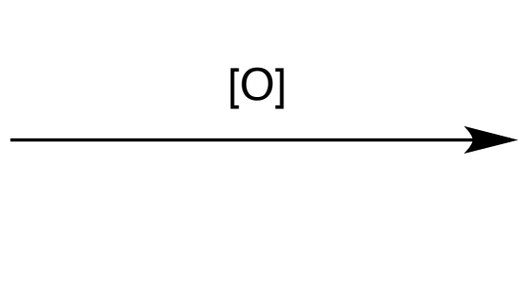



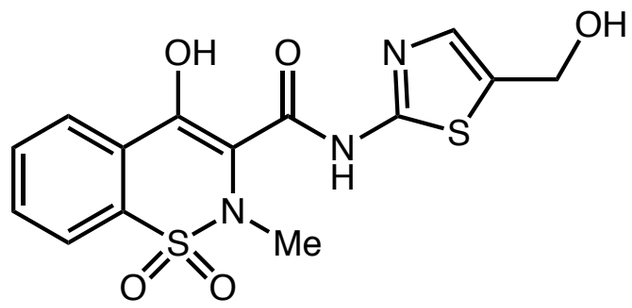




**meloxicam**

## Alternative oxidation



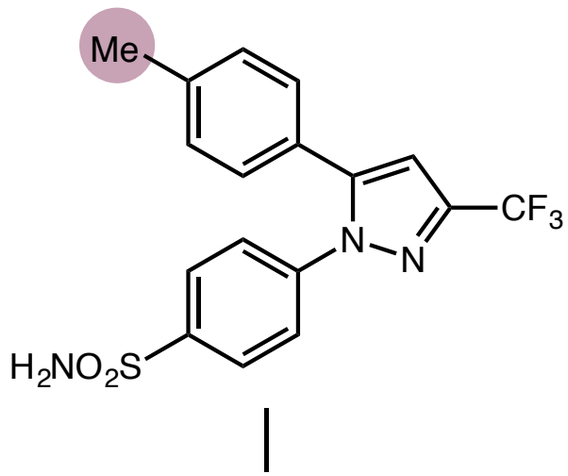




Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

# *Demystifying the Magic Methyl Effect*

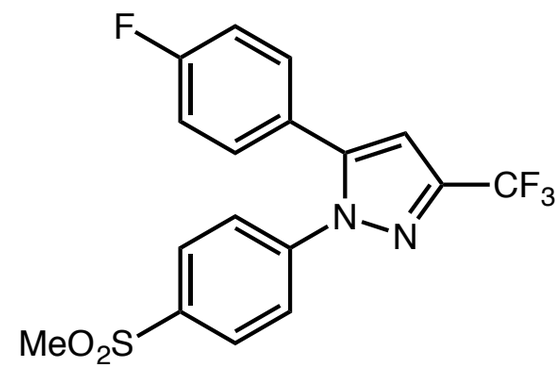
## ■ Oxidation of benzylic methyl groups




**celecoxib**

*anti-inflammatory drug*

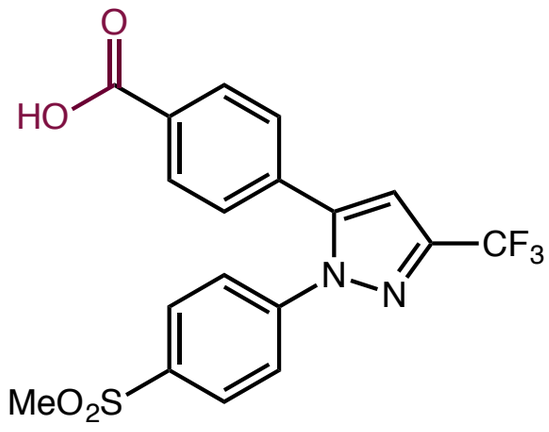
methylation to decrease half-life




*long half-life leads to accumulation of drug and possible side effects*



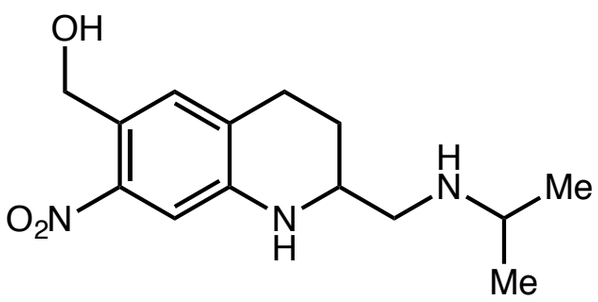

[O]




Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

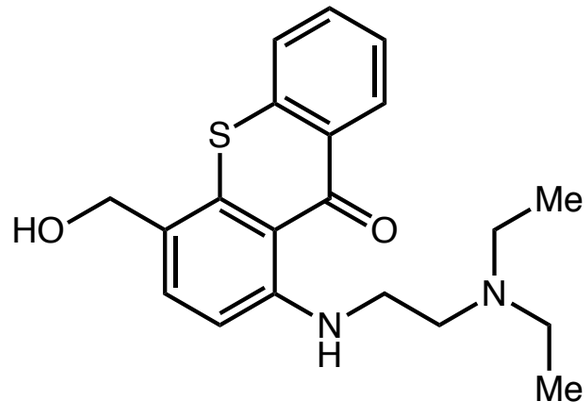
# *Demystifying the Magic Methyl Effect*

## ■ Prodrug example



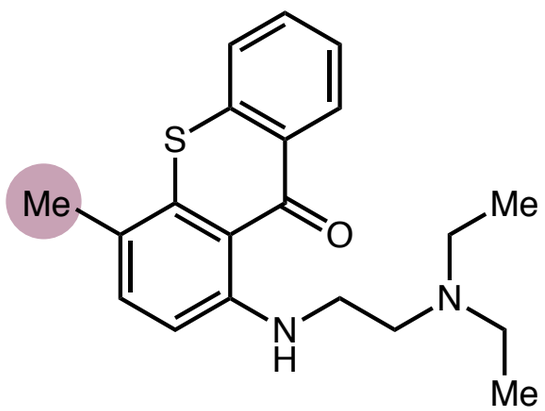

**oxaminiquine**
*antihelmintic drug*

increase potency

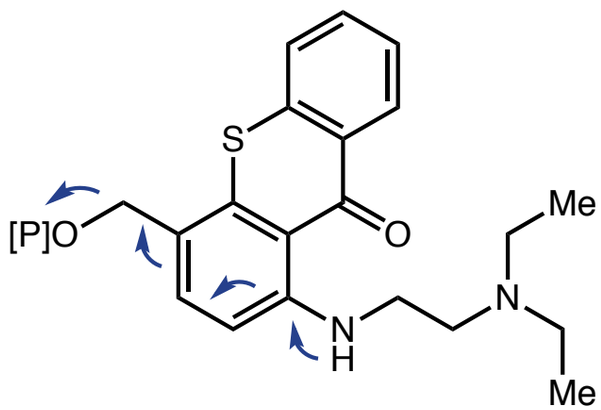



**hycanthone**

**in vivo**




*more lipophilic,*
*better bioavailability*

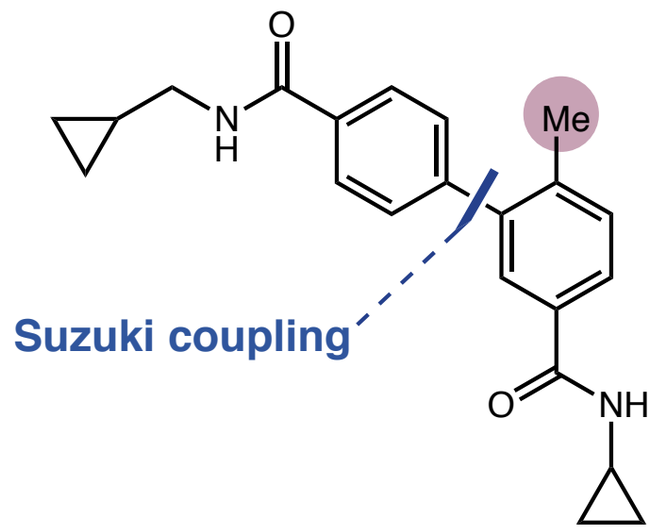


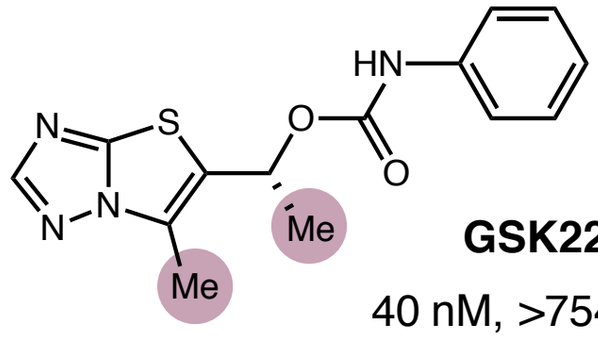

Barreiro, E. J.; Kummerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215-5246.

# *Demystifying the Magic Methyl Effect*

■ How are methyl groups typically installed?

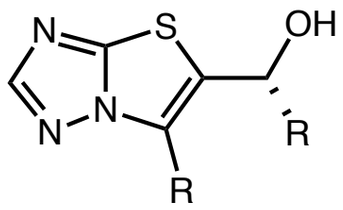
**De Novo Synthesis**



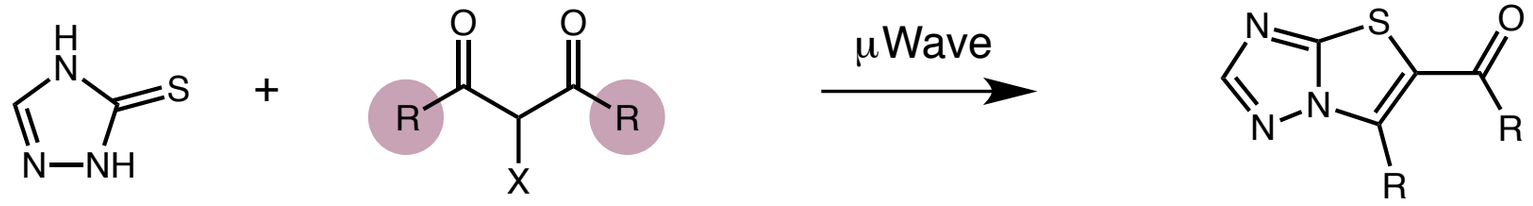

**GSK2210875**

40 nM, >754-fold boost




**A Call for C-H to C-Me transformations**

**selective reduction**

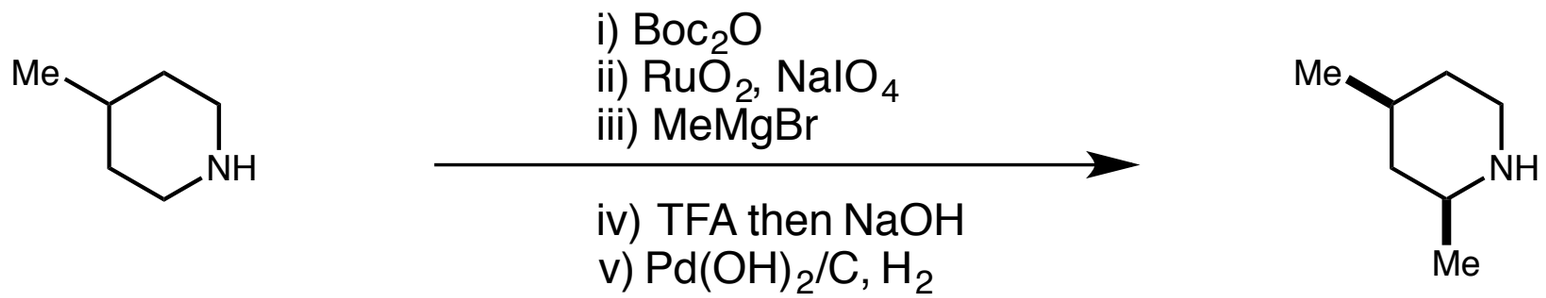



Pilla, M. et al. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7521-7524.

# *Demystifying the Magic Methyl Effect*

- How are methyl groups typically installed?

**A Call for C-H to C-Me transformations**




- Direct methylation will come in handy during fine-tuning stages of drug development
- Many cases where methylation of advanced intermediate only possible via de novo
- Payoff is unknown
- Need to explore methylated chemical space
- Recent advances made for $CF_3$, $CHF_2$, monofluorination - leaving Me behind


Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394-8395.
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

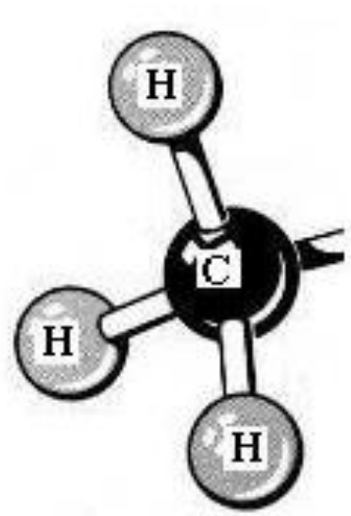
*Demystifying the Magic Methyl Effect*

## Modes of Action

***a combination of.....***

**Solubility**

**Conformation**



methyl group

**Binding Interactions**

**Metabolism**

***later.....***

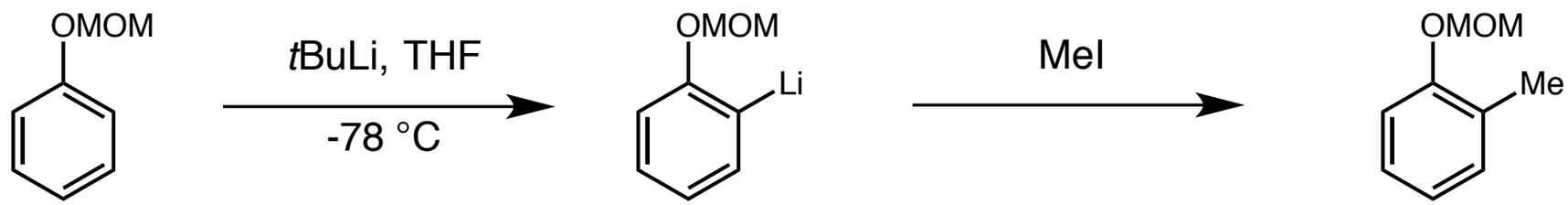
**Current Synthetic Methods**

# *Demystifying the Magic Methyl Effect*

## ■ Methylation of C($sp^2$)-H Bonds

### ■ Most acidic C-H via induction or *ortho*-direction

***Direct deprotonation via inductive effects:***

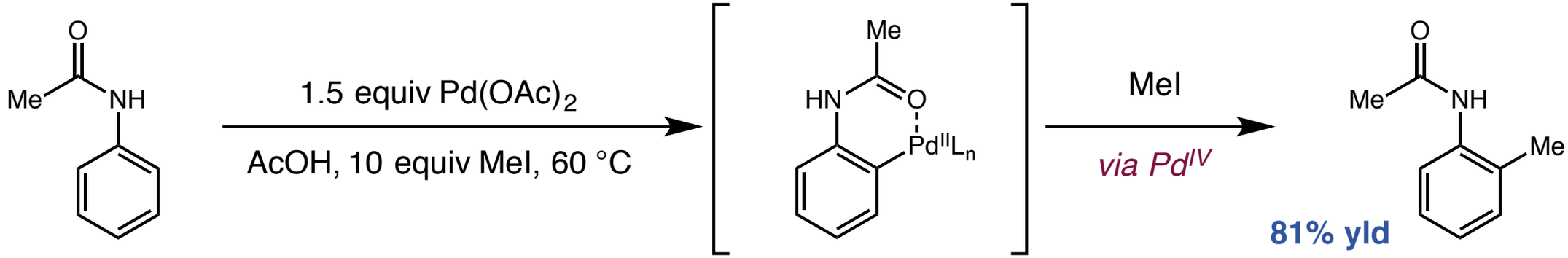



**Limitations: need base stable functional groups**

**Li-halogen exchange requires de novo synthesis**

### ■ directed C-H activation with transition metal

***First report of complementary acidic methodology:***





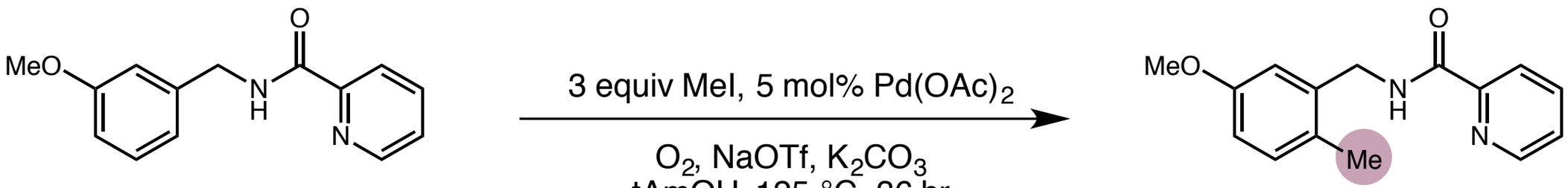
Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.
Tremont, S. J.; Rahman, H. U. *J. Am Chem. Soc.* **1984**, *106*, 5759-5760.

# *Demystifying the Magic Methyl Effect*

## Methylation of C($sp^2$)-H Bonds

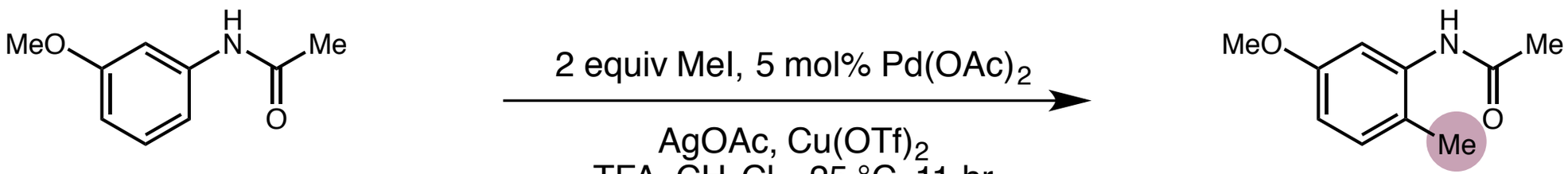
### Improvements with $Pd(OAc)_2$ and MeI

***catalytic $Pd(OAc)_2$:***




**90%**

***Ambient temperatures:***




**86%**

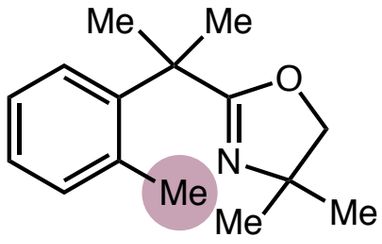

Jang, M. J.; Youn, S. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 2865-2866.
Zhao, Z.; Chen, G. *Org. Lett.* **2011**, *13*, 4850-4853.
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

# *Demystifying the Magic Methyl Effect*

## Methylation of C($sp^2$)-H Bonds

### Transmetalation reagents can be used

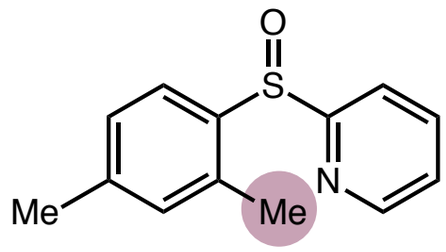
***various oxidants needed for metal turnover:***




**86%**

**$SnMe_4$**

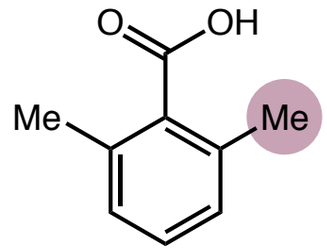
10 mol% $Pd(OAc)_2$,
BQ, $Cu(OAc)_2$
MeCN, 100 °C, 40 h



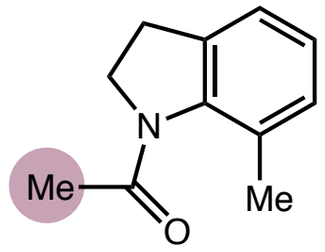

**62%**

**$MeB(OH)_2$**

10 mol% $Pd(OAc)_2$,
air, BQ, AgOAc
*t*AMOH, 100 °C, 20 h




**75%**



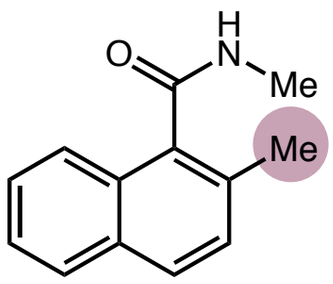

**83%**

**$MeBF_3K$**

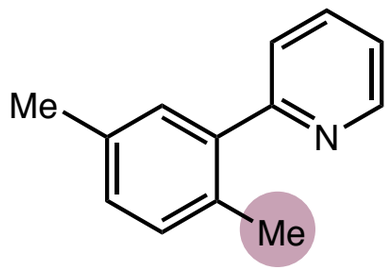
10 mol% $Pd(OAc)_2$,
$MnF_3$, AcOH
TFE/$H_2O$, 40 °C, 3h

**MeMgCl**

10 mol% $Co(acac)_2$
DMPU, THF, rt, 12 h




**68%**




**76%**

**MeCOOH**

2.5 mol% [{$Rh(CO)_2Cl$}$_2$],
$Boc_2O$, toluene,
140 °C, 24 hr

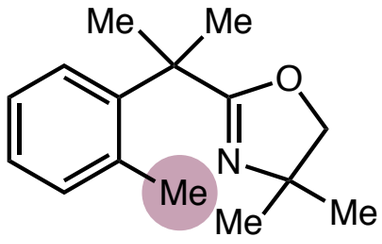

Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

# *Demystifying the Magic Methyl Effect*

## Methylation of C($sp^2$)-H Bonds

### Transmetalation reagents can be used

***various oxidants needed for metal turnover:***

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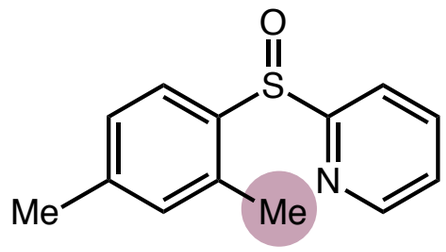
MeCN, 100 °C, 40 h

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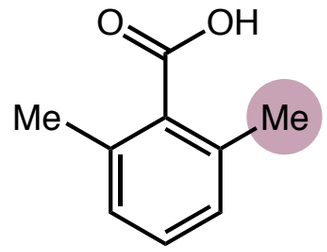
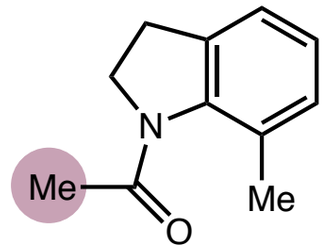
10 mol% $Pd(OAc)_2$,
air, BQ, AgOAc
*t*AMOH, 100 °C, 20 h




**75%**




**83%**

**$MeBF_3K$**

10 mol% $Pd(OAc)_2$,
$MnF_3$, AcOH
TFE/$H_2O$, 40 °C, 3h

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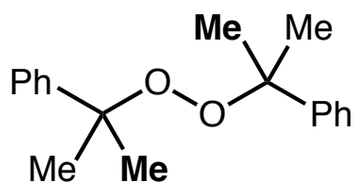
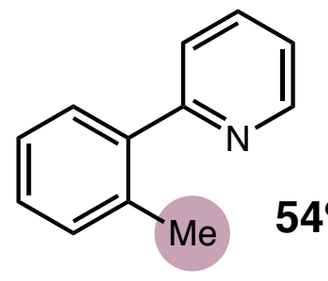



**peroxides as transmetallating reagents**

10 mol% $Pd(OAc)_2$,
neat,
140 °C, 12 h

β-methyl *elimination*

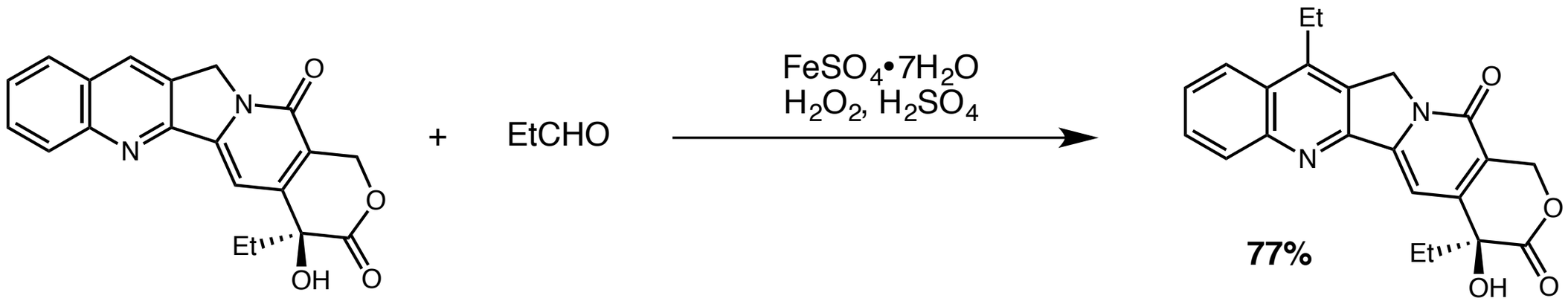



**54%**

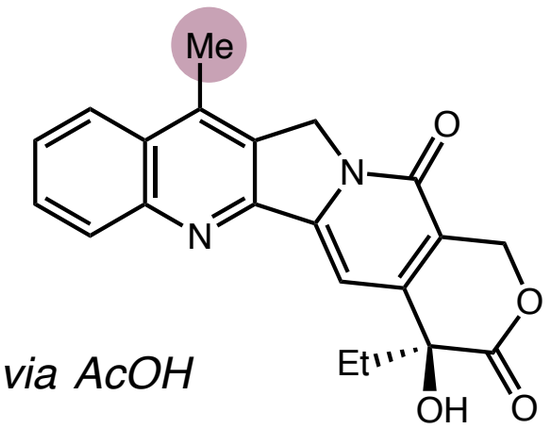
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

# *Demystifying the Magic Methyl Effect*

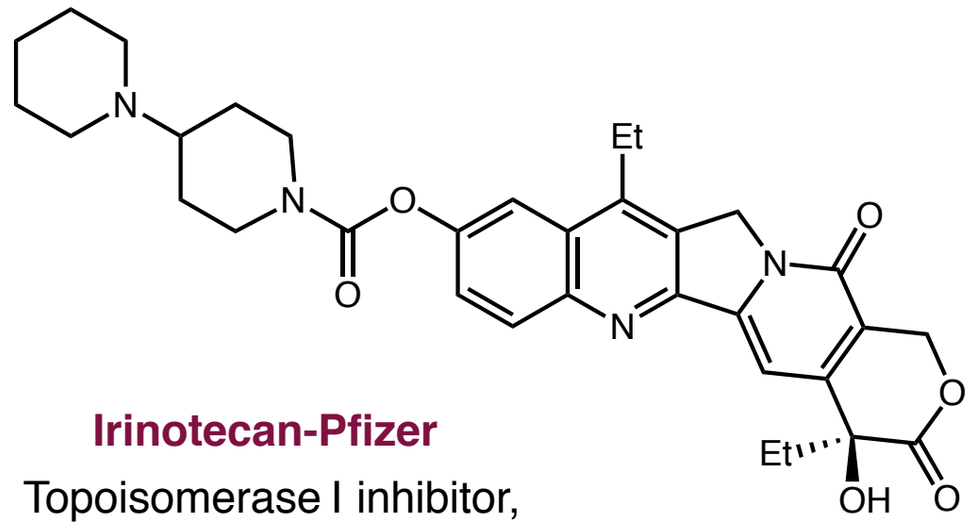
- Methylation of C($sp^2$)-H Bonds
  - Application of Minisci reaction




***easy installation of Me for SAR:***




*via AcOH*




**Irinotecan-Pfizer**

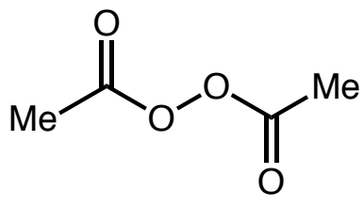
Topoisomerase I inhibitor,
cancer treatment


Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.
Duncton, M. A. J. *Med. Chem. Comm.* **2011**, *2*, 1135-1161.

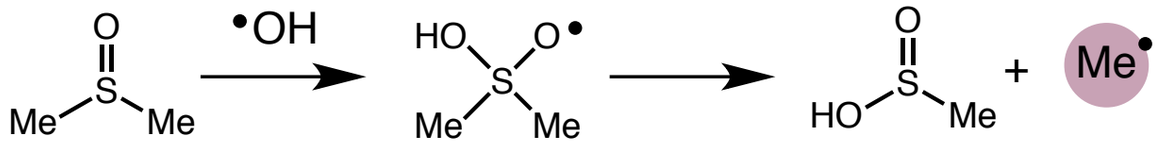
# *Demystifying the Magic Methyl Effect*

## Methylation of C($sp^2$)-H Bonds

### Me radical generation known to functionalize arenes



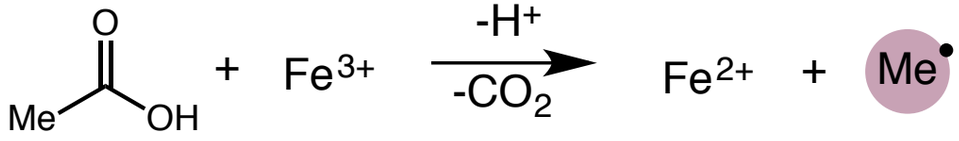

**diacyl peroxides**
**heat or hν**




**Fenton's Reagent with DMSO**
$FeSO_4 \bullet 7H_2O$, $H_2O_2$, DMSO

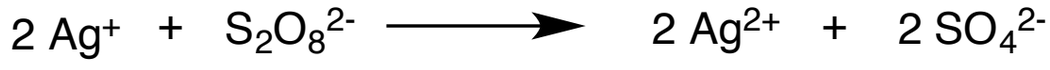
Me•

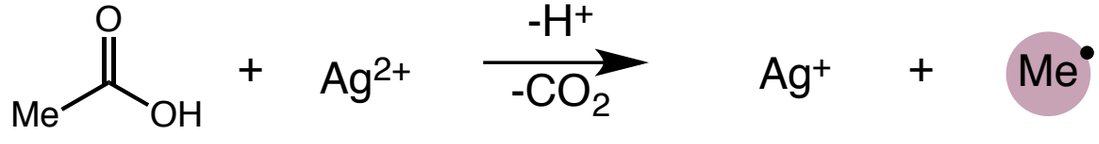
**Minisci with $Fe^{2+}$**
$FeSO_4 \bullet 7H_2O$, $tBuO_2H$, $H_2SO_4$


*carboxylic acid*

**Minisci with $Ag^+$**
$AgNO_2$, $(NH_4)_2S_2O_8$, $H_2SO_4$




*carboxylic acid*

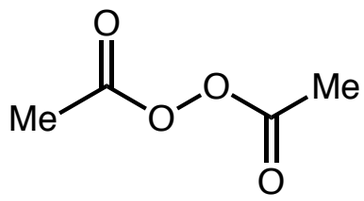

Giordano, C.; Minisci, F.; Tortelli, V.; Vismara, E. *J. Chem. Soc., Perkin Trans. 2* **1984**, 293.

Levy, M.; Szwarc, M. *J. Am. Chem. Soc.* **1955**, *77*, 1949.

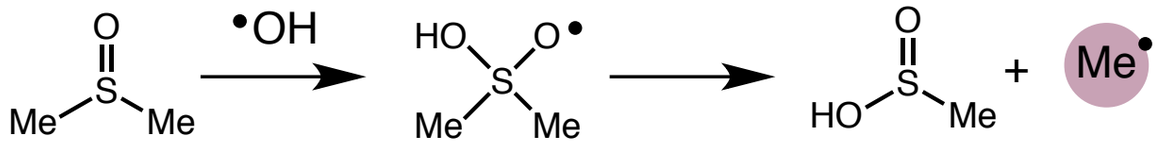
# *Demystifying the Magic Methyl Effect*

## Methylation of C($sp^2$)-H Bonds

### Me radical generation known to functionalize arenes




**diacyl peroxides**
**heat or hν**

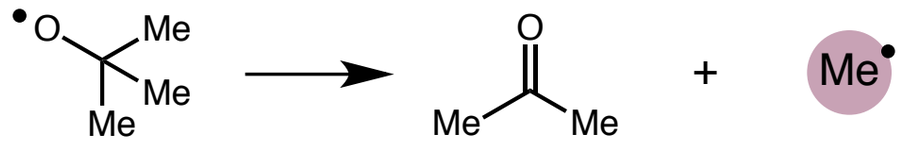



**Fenton's Reagent with DMSO**
$FeSO_4 \bullet 7H_2O$, $H_2O_2$, DMSO

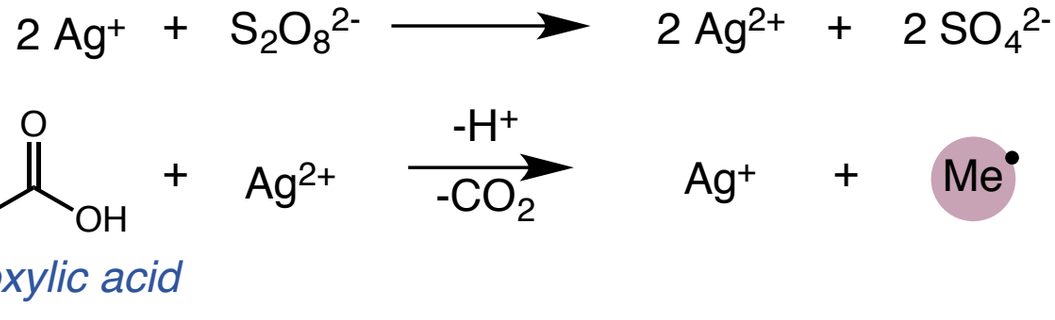
**Me•**

**Minisci with $Fe^{2+}$**
$FeSO_4 \bullet 7H_2O$, $tBuO_2H$, $H_2SO_4$


***or decomposition:***




**Minisci with $Ag^+$**
$AgNO_2$, $(NH_4)_2S_2O_8$, $H_2SO_4$




*carboxylic acid*

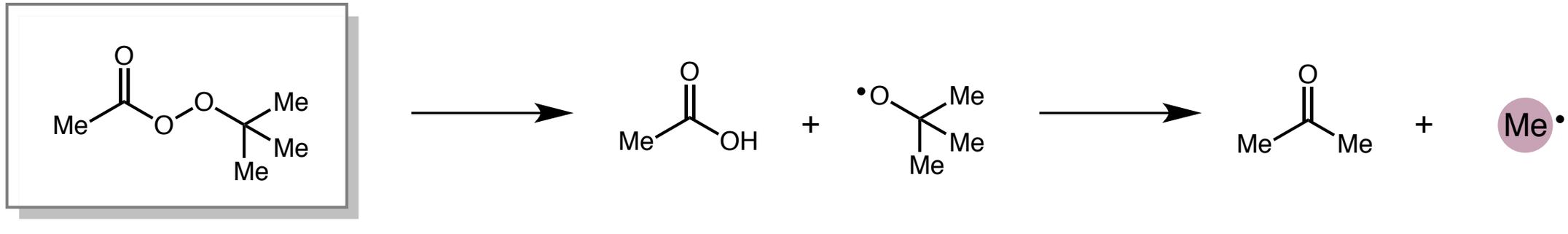

Giordano, C.; Minisci, F.; Tortelli, V.; Vismara, E. *J. Chem. Soc., Perkin Trans. 2* **1984**, 293.

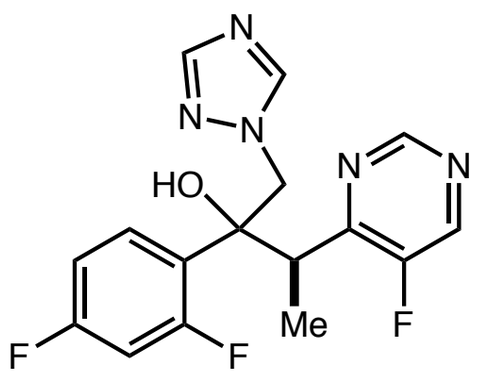
Levy, M.; Szwarc, M. *J. Am. Chem. Soc.* **1955**, *77*, 1949.

# *Demystifying the Magic Methyl Effect*

## ■ Methylation of C($sp^2$)-H Bonds

### ■ Various alkyl radical reagents



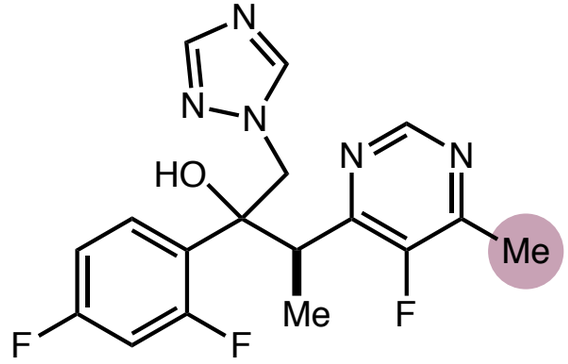




**Voriconazole**

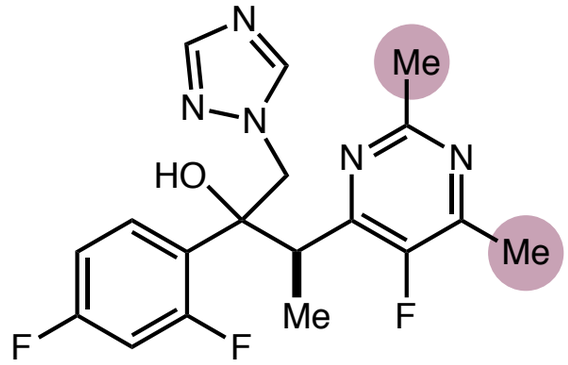
*anti-fungal*

$Ir(dFCF_3ppy)_2(dtbbpy)PF_6$

AcOO*t*Bu, visible light, TFA




**75% yld, 2.9:1**

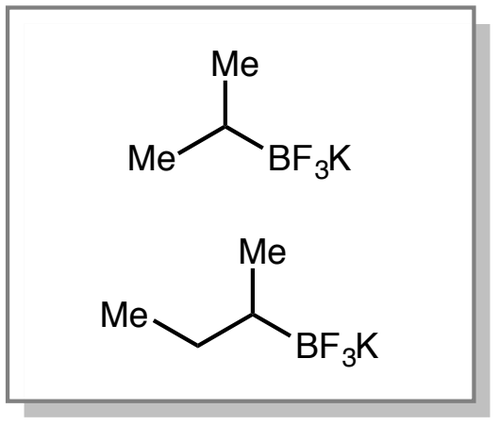


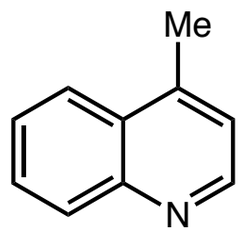

DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 4802-4806.

# *Demystifying the Magic Methyl Effect*

## ■ Methylation of C($sp^2$)-H Bonds

### ■ Various alkyl radical reagents

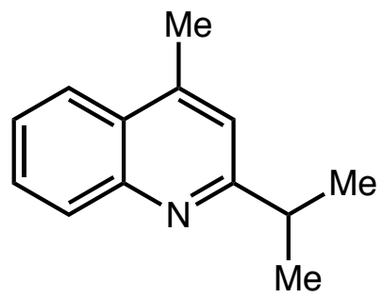


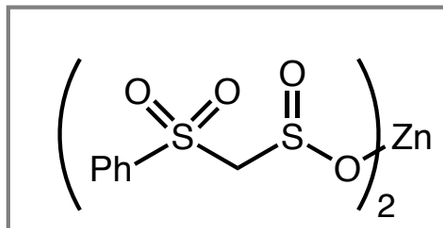

2.5 equiv $Mn(OAc)_3$
1 equiv TFA

$AcOH:H_2O$ 1:1,
50 °C, 18 hr

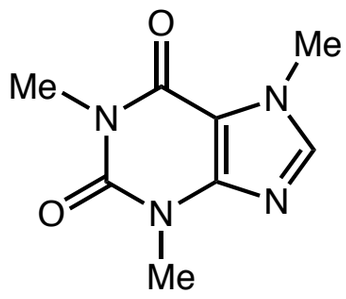
**no methyl examples**




**85%**

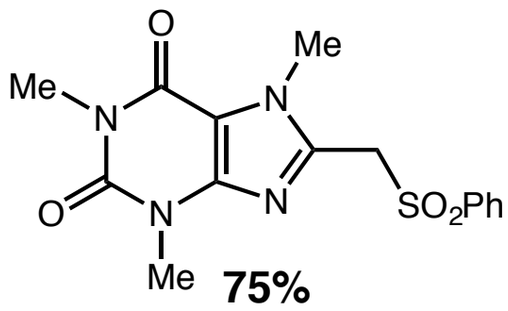



*1g/$205 Aldrich*
**PSMS**

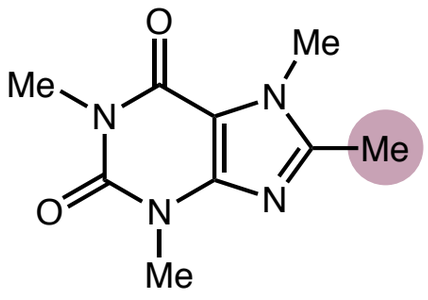



3 equiv PSMS

5 equiv TBHP
$PhCF_3/H_2O$, rt, 24 hr




**75%**



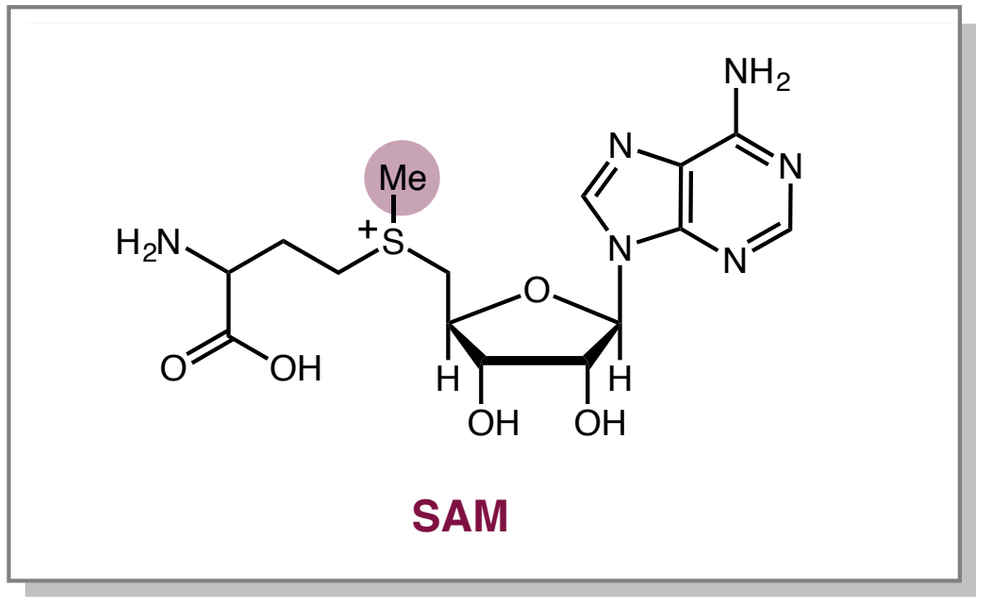

| | |
|---|---|
| A: Mg, MeOH, 50 C, 2h | 90% |
| B: SmI2, THF/H2O, rt, 30 min | 99% |
| C: Raney-Ni, EtOH, reflux, 2h | 93% |


Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852-1855.

Gui,J.; Baran, P. S. et al. *J. Am. Chem. Soc.* **2014**, *136*, 4853-4856.

# *Demystifying the Magic Methyl Effect*

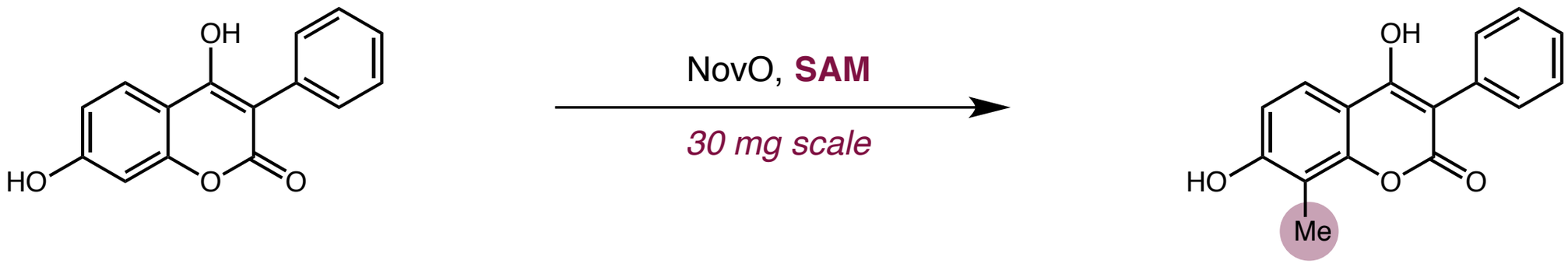
- Biocatalytic C-H methylation
  - S-Adenosylmethionine (SAM)- Nature's cofactor for methylation




**SAM**

***problems recycling cofactor***

***& is very costly***





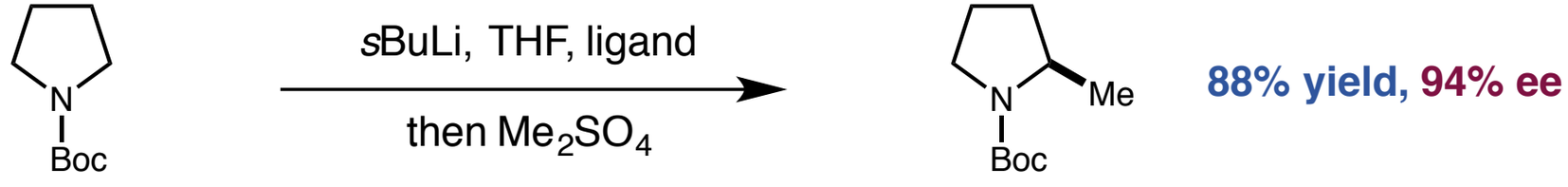
Stecher, H.; Tengg, M.; Ueberbacher, B. J.; Remler, P.; Schwab, H.; Griengl, H.; Gruber-Khadjawi, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9546-9548.
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

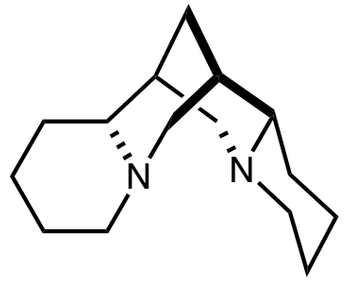
# *Demystifying the Magic Methyl Effect*

## ■ Methylation of C($sp^3$)-H Bonds

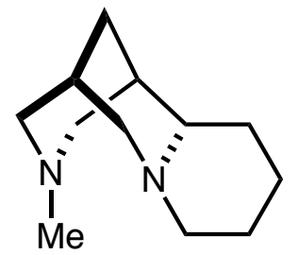
### ■ α-Heteroatom functionalization via most acidic CH

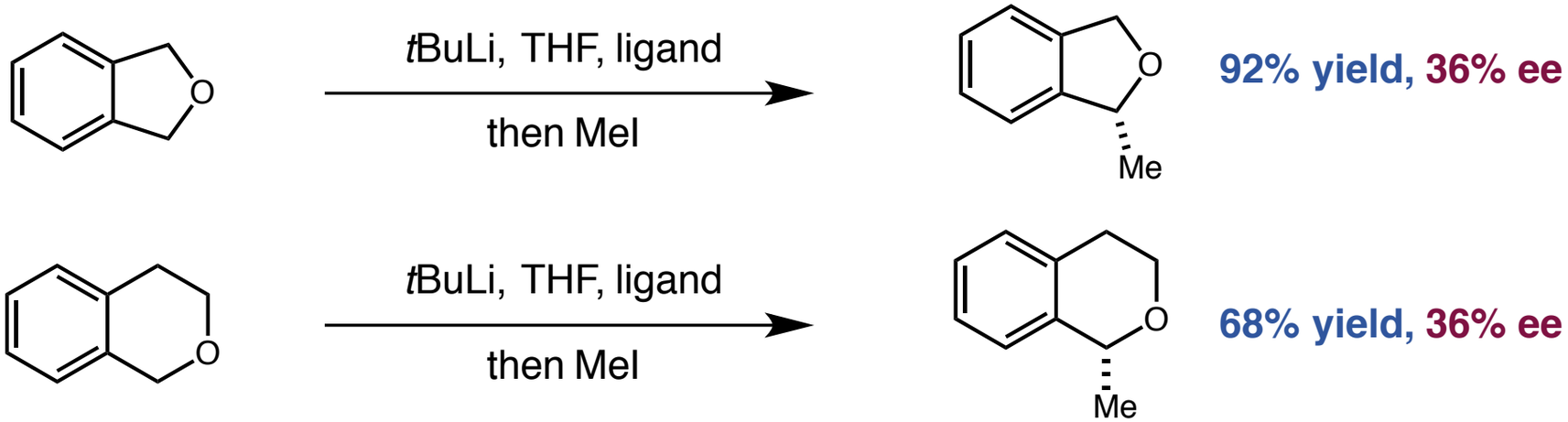
***An eye toward enantioselectivity:***

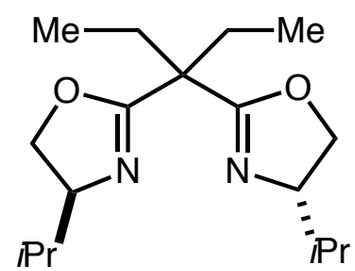



(-)-sparteine

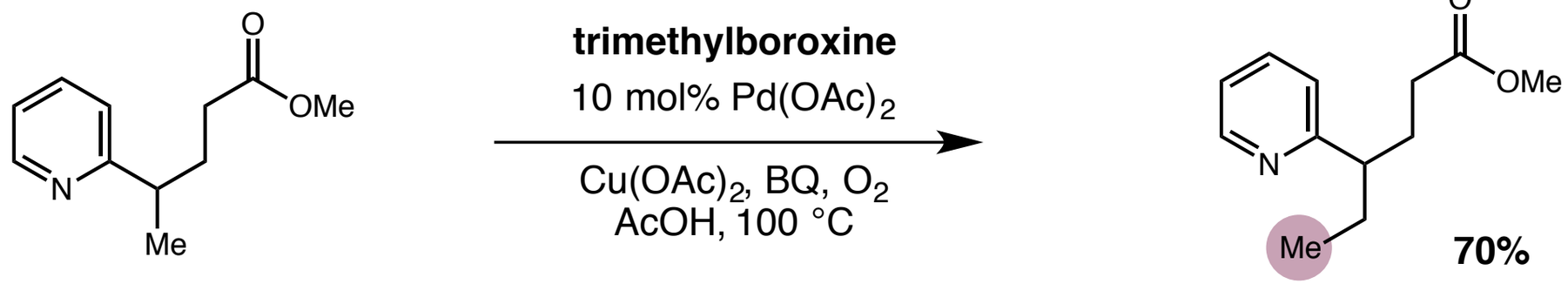




Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256-12267.

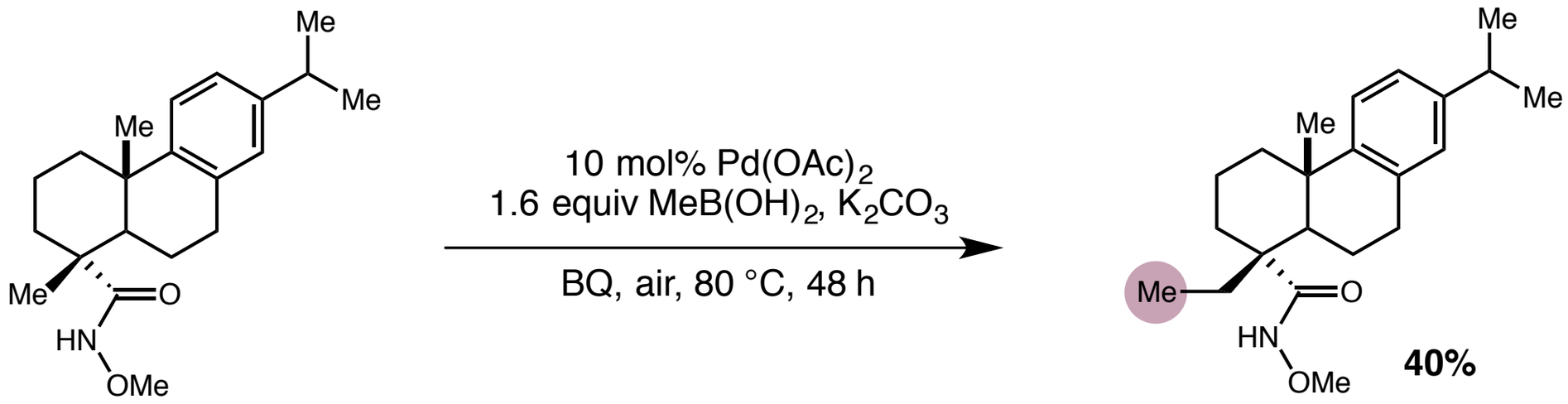
# *Demystifying the Magic Methyl Effect*

## ■ Methylation of C($sp^3$)-H Bonds

### ■ C-H activation examples - emerging interest




**favored alkylation of primary position**




**dehydroabietic acid**

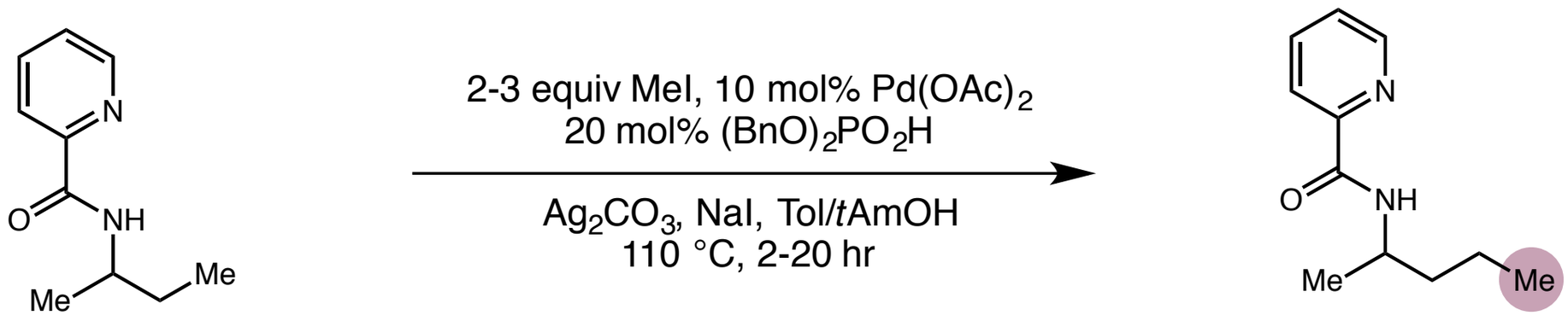
**other alkyl groups compatible with transformation for late-stage funcationalization**


Chen, X.; Goodhue, C. E., Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634-12635.
Wang, D.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190-7191.

# *Demystifying the Magic Methyl Effect*

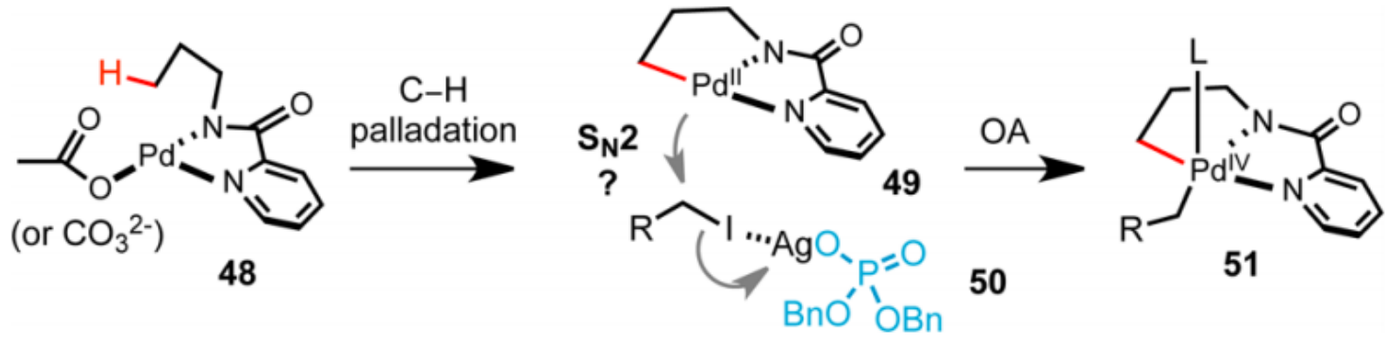
## ■ Methylation of C($sp^3$)-H Bonds

### ■ C-H activation examples - emerging interest




**86%**
**γ-Methylation**

**Scheme 1. Mechanistic Hypothesis**

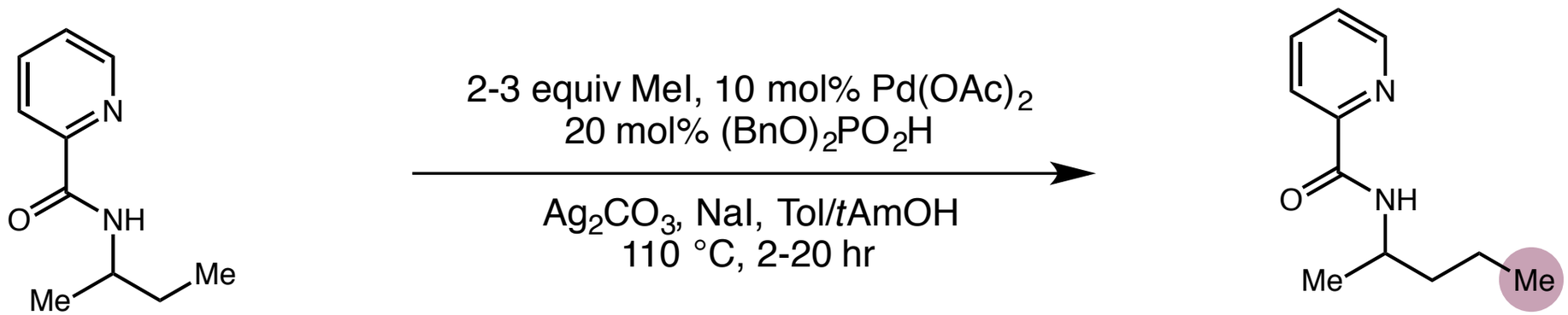



Zhang, S. Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Li, Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124-2127.

# *Demystifying the Magic Methyl Effect*

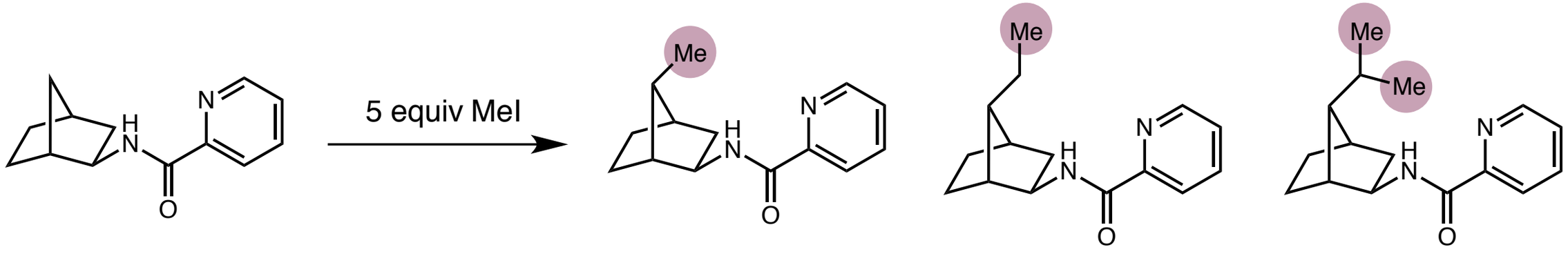
## ■ Methylation of C($sp^3$)-H Bonds

### ■ C-H activation examples - emerging interest




**86%**
**γ-Methylation**

***excess of MeI leads to multiple C-H activations:***



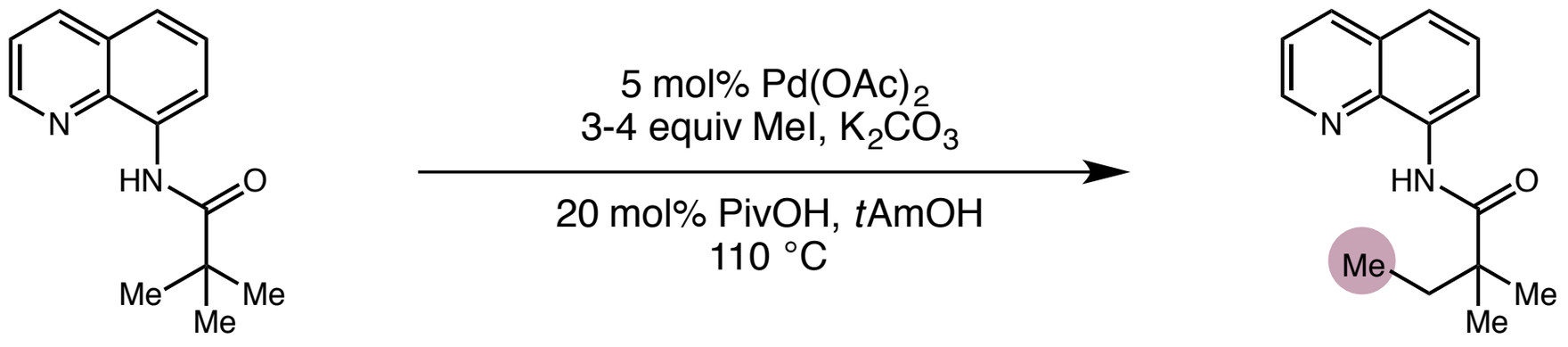

**77%**

Zhang, S. Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Li, Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124-2127.

# *Demystifying the Magic Methyl Effect*

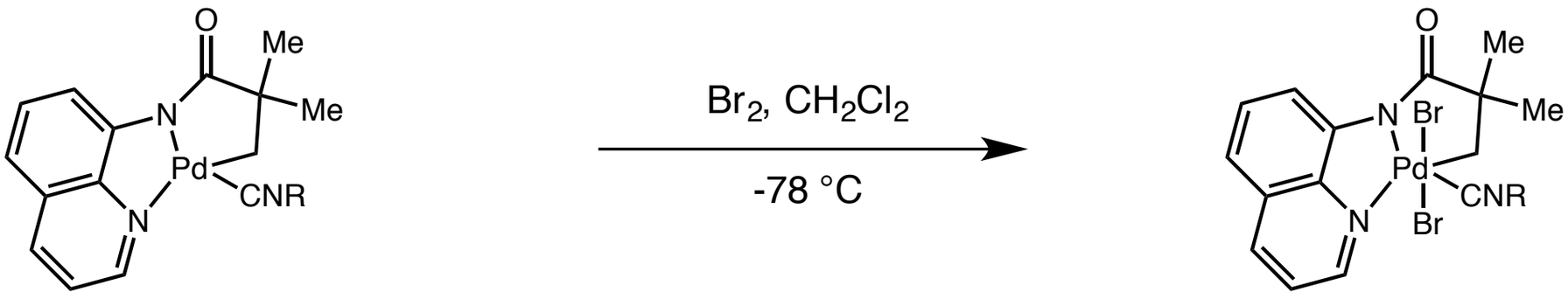
## ■ Methylation of C($sp^3$)-H Bonds

### ■ no silver salt oxidant




**68%**

***isolated palladacycle:***




**85%**

Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965-3972.

*"You sort of start thinking anything's possible if you've got enough nerve."*